

**Risk factors for Sexually Transmitted Infections in people living  
with Human Immunodeficiency Virus  
(Saskatoon health service data and Systematic review/Meta-  
analysis).**

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In partial Fulfillment of the Requirements for the Degree of Master of Science

In the Department of Community Health and Epidemiology in the College of  
Medicine University of Saskatchewan, Saskatoon

by

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## **Abstract**

**Background:** Globally over a million people are infected daily with a sexually transmitted infection (STI), giving rise to a major global health threat. Sexually transmitted infections have also been on the rise in Saskatoon Health Region (SHR). The region has the largest number of people living with HIV (PLWH) in the province of Saskatchewan. Globally, the prevalence of STIs have been reported to be high among PLWH. The diagnosis of other STIs in PLWH suggests the possibility that PLWH are putting non-infected individuals at risk of HIV infection. Thus, identification of subgroups of PLWH at risk of acquiring other STIs is essential to guide intervention programs, such as to prevent further transmission of HIV and other STIs. Studies exploring risk factors for STI acquisition amongst PLWH are not available in SHR, and limited in Canada overall.

### **Objectives:**

1. To explore whether either gender or IDU are risk factors for STI acquisition in the year before and after HIV diagnosis in SHR.
2. To determine if gender is a risk factor for acquiring STIs among PLWH in developed countries.
3. To determine if IDU is a risk factor for acquiring STIs among PLWH in developed countries.

**Methods: Objective 1:** Saskatoon Health Region health service data on PLWH with and without STIs during the years 2009 to 2014 were examined. Twenty-two PLWH with an STI diagnosis within a year before and after HIV diagnosis were compared to one hundred and thirty-three PLWH without an STI diagnosis for variables potentially associated with STI acquisition in HIV.

**Objective 2&3:** A systematic review and meta-analysis was conducted according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Effective Public Health Practice Project (EPHPP) recommendations. Its reporting was guided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies from developed countries addressing acquisition of other STIs in PLWH were identified. Relevant data were abstracted and differences in odds ratios (OR) across the studies and heterogeneity were examined using meta-analysis.

## **Results**

### **Objective 1:**

Multivariable analysis showed an association with marginal statistical significance between female gender (OR: 4.99; CI: 0.89-27.3) and the risk for STI acquisition in the year before and after HIV diagnosis in SHR. There was also a significant association between sex work (OR: 5.0; CI: 1.03 -24.6) and the risk for STI acquisition in PLWH during this period in SHR. No association was observed between IDU and the risk for STI acquisition in the year before and after HIV diagnosis in SHR (OR: 0.20; CI: 0.03-1.2). No interaction was observed between the variables.

**Objectives 2 & 3:** Ten articles were reviewed for the gender analysis. The pooled OR for HIV-infected females acquiring other STIs compared to males was 1.38 (CI: 0.75-2.55), with a high heterogeneity of  $I^2 = 96\%$ . For the IDU analysis, six articles were reviewed. The pooled OR for IDUs acquiring other STIs compared to non-IDU was 0.71 (CI: 0.4-1.29), with a high heterogeneity of  $I^2 = 85\%$ .

**Conclusion:** In the face of scarce resources public health practitioners should prioritize programs to address HIV subgroups more at risk for STI acquisition. Special programs may also be necessary to reach certain high-risk groups.

**Keyword:** HIV, Sexually Transmitted Infections, Injection Drug Use, Gender, Developed Countries

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## **Dedication**

This thesis is dedicated to God, my pillar and strength.

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## **List of abbreviations**

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
CF	Conceptual framework
CI	Confidence interval
DA	Dissemination area
DI	Deprivation index
EPHPP	Effective public health practice project
FSW	Female sex worker
HIV	Human immunodeficiency virus
HIV/STI	HIV and STI co-infection
HRQOL	Health-related quality of life
IDU	Intravenous drug user
iPHIS	Integrated public Health Information System
MSM	Men having sex with Men
MOOSE	Meta-analysis of observational studies in epidemiology
OR	Odds ratio
PHN	Personal health number
PHO	Public health observatory
PLWH	People living with HIV
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QMATLOC	Local material deprivation quintile
QSOCLOC	Local social quintile
Q	Quintile

RevMan	Review Manager 5.3
SBR	Sexual behavioral risk
SES	Socioeconomic status
SHR	Saskatoon health region
SIF	Supervised injection facilities
STI	Sexually transmitted infection
SW	Sex worker
TOTDEPLOC	Total local (combination of material and social scores)
VL	Viral load

## **Chapter 1: Introduction**

This section provides the study rationale, gives background on the association between human immunodeficiency virus (HIV) and STIs. It also states the purpose and objectives of the study. Lastly, it describes the theoretical perspective and conceptual framework (CF) which was used to guide the study.

### **1.1 Study rationale**

The effect of STIs on health morbidity and mortality cannot be overemphasized, with over 340 million newly diagnosed STIs (other than HIV) in 1999. (1) The presence of other STIs among PLWH contributes to further transmission of HIV. (2) More than a million people are infected daily with an STI, giving rise to a major global health threat. (3) Despite the availability of antiretroviral therapy (ART) for PLWH, coexisting STIs remain a major risk factor to be considered for HIV transmission. (2) The incidence of STIs in PLWH was observed to be on the rise since early 2000's. (2, 4) This could be because PLWH are living longer due to the advent of ART or even decrease stigma to HIV.

A synergistic epidemic is said to occur between HIV and other existing STIs partly as a result of high-risk health behavior found among people with HIV and other STIs.(4, 5) Some high-risk behaviors include sex work, unsafe sex with casual and multiple partners, and sexual practice influenced by substance abuse.(4) Studies in the past had reported that STI coexisting with HIV can serve as a marker for continued sexual risk behavior.(6-9) Several studies had reported the presence of other STIs in PLWH.(6-10) Kalichman *et al.* (2011) recorded a co-infection prevalence of 16.3%, with median prevalence of 9.5%, 9.5% and 5% for syphilis, gonorrhea and chlamydia respectively.(10)

Some studies documented an increased risk of HIV transmission when the infection co-existed with other STIs, especially in the presence of inflammation and ulcers. (11-13) This increases the probability of transmission of HIV and susceptibility to the virus. Co-infection with STIs is a recognised threat to the health of PLWH.(10) The presence of

STIs among this population increases the HIV viral load (VL) in both genital and anal secretions. (5, 12, 14) Generally, the concentration of HIV VL is lower in genital secretions compared to blood plasma, but with STI and HIV co-infection this is usually reversed.(10) The rise in VL in PLWH may be due to a number of factors, of which co-infection with other STIs plays a significant role. (2- 5, 12)

A study reported that HIV positive men with urethritis had an increased HIV VL in their semen, with their VL being eight times more compared to HIV positive men without urethritis.(12) After treating urethritis in these men, their semen VL was found to decrease tenfold compare to pre-treatment levels.(12) The increase HIV transmission is particularly higher in the presence of STI with inflammation and ulcer, and this increases infectiousness of the virus and susceptibility to HIV infection.(4, 13) The probability of HIV transmission increases with a rise in VL. For example, 100,000 viruses per ejaculation has the probability of HIV transmission of 1 in 100 episodes of intercourse compared to 1,000 viral copies which has a probability of 3 HIV transmission per 10,000 intercourse episodes. (5, 14) The presence of STIs not only increases VL in affected patients but it also suppresses the CD4 counts (15), which increases susceptibility of an HIV-infected person to another STI. The alteration of these two clinical factors increase the risk of transmission of HIV especially in PLWH who are not on ART. (15) This evidence has been supported by other studies. (16–20)

Sexually transmitted infection co-existing with HIV has also been reported to hamper the ability of antiretroviral therapy (ART) to reduce genital infectiousness in about 15% of PLWH on treatment.(11) Sadiq and his colleagues backed up this finding in a research in 2005.(21) From the above discussion, we can observe that the overall health of PLWH may be hampered by co-existence of STIs.(22) This is particularly because it is more challenging to treat PLWH with a suppressed immune status.(22)

A mathematical equation developed by May and Anderson in 1987 can be used to determine the transmission of STIs in PLWH. (11, 13)

$$R_0 = \beta DC$$

$\beta$  = Probability of transmission,

D = Duration of infectiousness and



C = Measure of number of susceptible individuals in contact with infected person.

The three determinants of transmission of STIs in PLWH ( $\beta$ , D, C), do vary in distribution from one group of people to another (11), thus pointing out the reasons STIs behave differently in these groups.(11) The determinants are greatly influenced by multiple factors which includes social, economic, demographic, cultural, and behavioral factors at both individual and population level.(11) In view of this, we need to decipher which of these factors are drivers for the acquisition of STIs amongst PLWH in different contexts and understand how they influence each other.(11)Co-infection between HIV and other STIs affect the risk of transmission of both diseases.(23) Assessing a temporal relationship between HIV and other STIs is difficult because some STIs only become symptomatic upon diagnosis of HIV infection.(24) This emphasizes the need to routinely screen for STIs in PLWH.(24) Despite the fact that research is limited in this area, some papers have highlighted factors contributing to the risk of acquiring STIs in PLWH.(10,24-27) These factors include the ability of HIV infection to suppress the immunity of PLWH, thus increasing their susceptibility to acquire STIs.(10) Risky sexual behavior such as unprotected sex and having multiple sexual partners were also found to contribute to acquiring STIs in PLWH.(10, 24-27) Previous STIs also contribute to the acquisition of STIs in PLWH, especially when these STIs are undiagnosed and untreated.(10, 24-25) Almost a third of clients with HIV and STI co-infection (HIV/STI), in a study conducted in Spain, had a previous STI history. (28) The odds of having co-infection with previous STI in the study was four times more than individuals without previous STI. (28)

Risk of STIs transmission in PLWH was also reportedly affected by younger age, CD4 counts, VL, use of illicit drugs, alcohol and lack of social support. (25-27) Prevalence varies by study for STIs diagnosed among PLWH. Hague *et al.* (2011) reported STI co-infections in PLWH, among these, 58.5% were gonorrhea, 26.4% were syphilis, and 15.1% were chlamydia (6). While Asavapiriyant *et al.* (2013) observed 6.6% co-infections with chlamydia, 1.0%, with gonorrhea, and 0.7%, with syphilis.(29) A Canadian study by Romanoski *et al.* (2009) reported that 54% of these patients had co-infection with genital herpes.(31) About 50% of new cases of syphilis in Canada were found in PLWH.(31) Recent studies have indicated that prevention of HIV transmission is better achieved when targeted at PLWH, as they are the main source of transmission.(4) This type of prevention is referred to as positive prevention.(4) With the recent economic crisis information on factors contributing to the spread of new HIV infection can

inform decisions about resource allocation to support priority prevention programs in combating spread of infection.(32) The direct cost of HIV to Saskatchewan's health care system is estimated at about forty million dollars while indirect cost is approximately 2.4 times that of direct cost.(33)

HIV prevention programs globally do not include routine screening for STIs in PLWH. (34) Generally, data for STIs are underreported, and this makes it challenging to tackle factors contributing to STIs transmission. (34) The lack of STIs screening might have impacted data reporting negatively. HIV transmission will increase when we fail to recognise that its co-occurrence with STIs will reduce the benefit of ART in prevention and treatment of HIV infection. (10)

## **1.2 Study purpose**

Due to the paucity of studies on STI acquisition amongst PLWH in SHR, and Canada at large, this study aimed to explore risk factors for STI acquisition in PLWH in SHR. This will be addressed in two manuscripts. The first manuscript will explore whether either gender or IDU are risk factors for STIs acquisition in the year before and after HIV diagnosis in SHR. Given the limitation of SHR health service data on the dependent variable and the limitation of the available data on potential risk factors, the second manuscript will involve a systematic review and meta- analysis. This review will explore studies addressing risk factors contributing to STI acquisition among PLWH in developed countries. The systematic review solely explored STI acquisition after HIV diagnosed due to the paucity of literature addressing STI acquisition pre-HIV diagnosis. Developed countries were used for the analysis because studies exploring risk factors for acquiring STIs in PLWH were also limited in Canada. These countries were considered for analysis as their context with respect to STI acquisition amongst PLWH may be comparable to Canada.

### **Study Objectives:**

1. To explore either gender or IDU as risk factors for STIs acquisition in the year before and after HIV diagnosis in SHR.
2. To determine if gender is a risk factor for acquiring STIs among PLWH in developed countries.

3. To determine if IDU is a risk factor for acquiring STIs among PLWH in developed countries.

### **1.3 Theoretical perspective and conceptual framework**

Several theoretical perspectives have been created to explain patterns of disease in population health. A number of these theories have been applied in HIV/AIDS research, one of which is the biomedical model.

The core of the biomedical theory places emphasis on biological and individual-level factors to explain risk of HIV and STI transmission.(35) This model regards social factors as secondary or even unimportant in the transmission of HIV and other STIs.(35) Biological factors include genetic make-up and susceptibility, disease etiology and mechanism.(35) It regards individuals as free beings who are capable of making healthy behavioral choices while ignoring the impact of the socio-economic and political environment on risk factors that contributes to the acquisition of HIV and other STIs.(35) As a result, research and preventive programs based on the biomedical model are individualistic centered.(35) Data are gathered on individuals living with or exposed to HIV and scarcely ever include contextual factors.(35) Prevention programs based on this model, such as condom distribution and needle exchange programs are also targeted at the individual.(35)

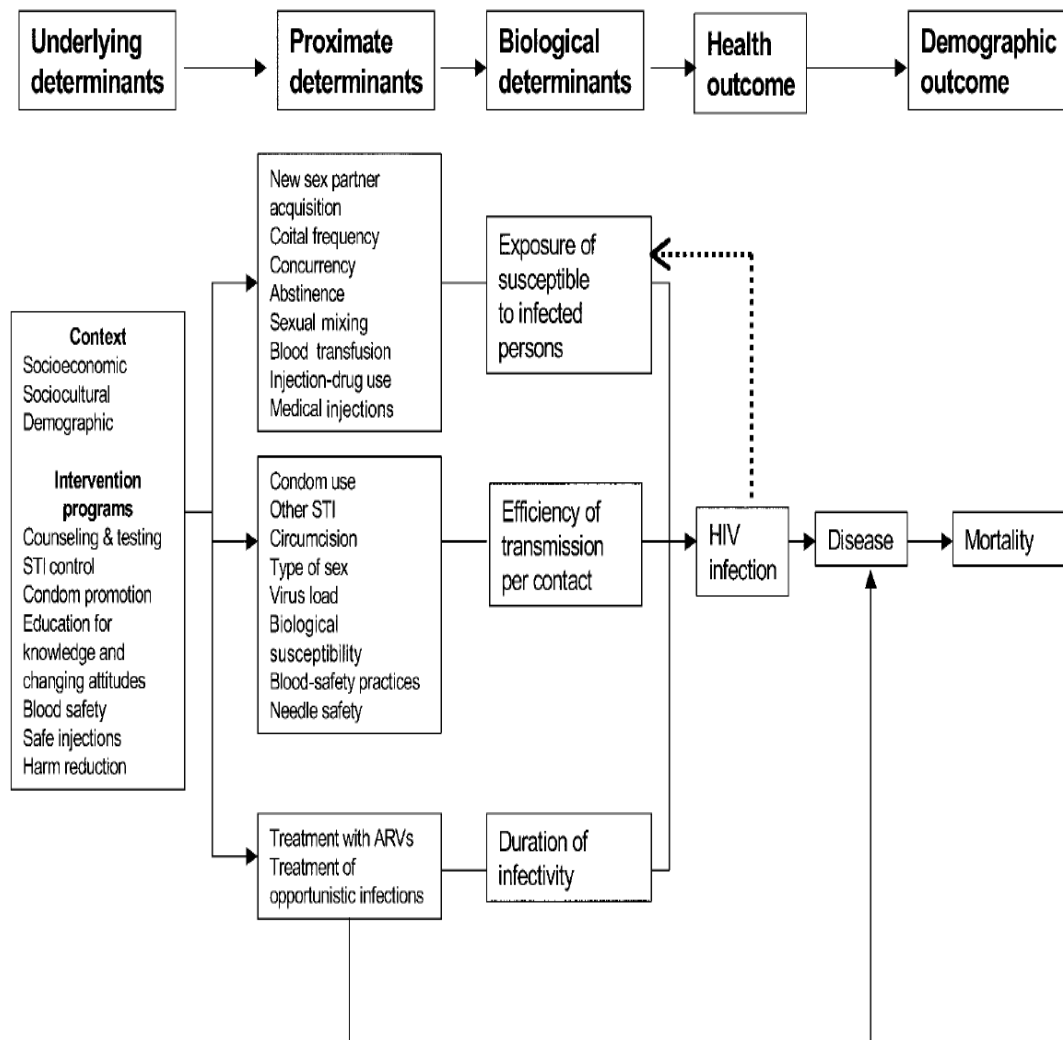
In contrast, social production of disease theory “conceptualizes determinants of disease distribution as economic and social relationships forged by a society's political and economic structure”.(36, p.108) These relationships are being channelled via various groups classified by socio-economic class, gender, age and ethnicity.(36) The presence of social groups in this relationship brings about inequalities amongst the various groups in their health and well-being.(36) For example, social production of disease theory, explains “how gender-based economic inequalities may affect women's ability to determine sexual uses of their bodies” (36, p.108), which could lead to their risk of acquiring HIV and other STIs. HIV research based on this theory underscores the association between increase STI transmission and groups defined by low socio-economic status and racial discrimination. (36) Preventive programs based on this theory emphasize social and political policies such as making available employment, low-income housing, and affordable education, stating these factors as key to winning the battle of STIs transmission.(36)

This study recognises the role that both biological/individual factors and contextual factors (socio-economic factors) plays in the distribution of health and diseases, but refutes the notion that the different factors operate independently in the transmission of disease (HIV and other STIs). The researcher believes individuals are greatly impacted by their contextual factors, and also that everyone has a role to play in managing their health. In other words, the two theories discussed above are mutually inclusive in the explanation of distribution of health and diseases.

### **Conceptual framework**

Accordingly, the Proximate-Determinants Framework will guide the study. The conceptual framework (CF) was used by Boerma and Weir in 2005, to study distribution and determinants of HIV and other STIs. (37) The framework identifies that biomedical and contextual factors are both important in the transmission of HIV and other STIs.(37) It also shows important determinants to consider in HIV and other STIs transmission, explaining the association between these determinants.(37) Emerging evidence emphasizes the role of STIs in HIV transmission. This transmission is not affected by individual level factors alone but also by social determinants of health such as income, employment, and housing. Unemployed people may lack material resources to provide shelter and therefore increase exposure to high-risk behavior and risk of HIV infection.

The framework illustrates three determinants, which are underlying, proximate, and biological with health and demography as outcomes.



**Figure 1.1: Proximate-determinants conceptual framework for factors affecting the risk of sexual transmission of HIV. (38)**

Underlying determinants comprise of contextual factors (sociocultural, socioeconomic, demography) and intervention programs. (37) In this study, socioeconomic factors will be depicted by social quantiles, which is a proxy for income, education and employment in SHR, sociocultural by ethnicity, and demography by age and gender. These contextual factors impact the proximate determinants leading to exposure and transmission of HIV and other STIs. In order for these contextual factors to influence HIV/STI transmission, they are obligated to act on the

proximate determinants as illustrated in Figure 1.1. This study will not be focussing on the intervention programs.

Proximate determinants are basically made up of behavioral and biological elements. (37) It influences biological determinants, which in turn affects the rate of transmission of HIV and other STIs. (37) Behavioral factors such as IDU, MSM, heterosexual practice and sex work will be considered in this study but biological factors (VL and biological susceptibility) will be excluded from this discussion.

Biological determinants are factors that influence the reproductive number of an infection, regulating HIV and STI prevalence in the population. (37) This subsequently leads to disease and death as displayed by the arrows in Figure 1.1. This reproductive number is the product of three biological determinants, previously discussed in Section 1.1 where  $R_0 = \beta DC$ ;  $\beta$  = Probability of transmission,  $D$  = Duration of infectiousness and  $C$  = Measure of number of susceptible individuals in contact with infected person.

A rise or decline in any of these three factors will result in increase or decrease in transmission of HIV and other STIs. This research will not explore these determinants nor demographic or mortality outcomes.

Overall, I believe the proximate determinants framework will adequately guide the study. This is because it acknowledges both population level factors/underlying determinants (socioeconomic, sociocultural, demography) and individual factors/proximate determinants (MSM, IDU, heterosexual, STI) as important risk factors in the transmission and co-infection of HIV and other STIs. It also centers on the sexual transmission of infection, which is common to both HIV and other STIs.

#### **1.4 Chapter summary**

This chapter described the rationale of the study and pinpointed the aim and objectives of the study. It further described the theoretical perspective and conceptual framework used for the study.

## 1.5 References

1. Lewis DA, Latif AS, Ndowa F. WHO global strategy for the prevention and control of sexually transmitted infections: time for action. *Sexually transmitted infections*. 2007 1; 83(7): 508–09.
2. Sprenger K, Evison JM, Zwahlen M, Vogt CM, Elzi MV, Hauser C, et al. Sexually transmitted infections in HIV-infected people in Switzerland: cross-sectional study. *PeerJ* 2014; 2:e537.
3. Zhao Y, Luo T, Tucker JD, Wong WC. Risk factors of HIV and other sexually transmitted infections in China: A Systematic Review of Reviews. *PLoS One* 2015; 10(10):e0140426.
4. Centers for Disease Control and Prevention. Sexually Transmitted Disease and HIV – CDC Fact Sheet. Atlanta: Centers for Disease Control and Prevention; 2014. [Cited 2015 May 05]. Available from: <http://www.cdc.gov/std/hiv/hiv-std-factsheet-dec-2014.pdf>
5. Hughes G, Field N. The epidemiology of sexually transmitted infections in the UK: impact of behaviour, services and interventions. *Future Microbial* 2015; 10(1): 35–51.
6. Hague JC, Muvva R, Miazad RM. STD coinfection and reinfection following HIV diagnosis: Evidence of continued sexual risk behavior. *Sex Transm Dis* 2011; 38 (4):347-8.
7. Rieg G, Lewis RJ, Miller LG, Witt MD, Guerrero M, Daar ES. Asymptomatic Sexually Transmitted Infections in HIV-Infected Men Who Have Sex with Men: Prevalence, Incidence, Predictors, and Screening Strategies. *Aids Patient Care STDs* 2008; 22 (12): 947-54.
8. Manning SE, Pfeiffer MR, Nash D, Blank S, Sackoff J, Schillinger J. Incident Sexually transmitted infections among Persons Living with Diagnosed HIV/AIDS in New York City, 2001–2002: A Population-Based Assessment. *Sex Transm Dis*, 2007; 34 (12):1008–15.
9. Hu QH, Xu JJ, Zou HC, Liu J, Zhang J, Ding HB, et al. Risk factors associated with prevalent and incident syphilis among an HIV-infected cohort in Northeast China. *BMC Infect Dis*, 2014; 4(1): 658.

10. Kalichman SC, Pellowski J, Turner C. Prevalence of sexually transmitted co-infections in people living with HIV/AIDS: systematic review with implications for using HIV treatments for prevention. *Sex Transm Infect* 2011, 87 (3):183-90.
11. Gomez G B, Ward H, Garnett G. P. Risk pathways for gonorrhea acquisition in sex workers: can we distinguish confounding from an exposure effect using a priori hypotheses? *J Infect Dis* 2014; 210 (2): S579-85.
12. Sheth P, Thorndycraft B. Fact sheet: sexually transmitted infections and HIV transmission. Toronto: Canadian Aids Treatment Information Exchange; 2009. [Cited 2015 May 04]. Available from: <http://www.catie.ca/en/fact-sheets/epidemiology/sexually-transmitted-infections-and-hiv-transmission>.
13. Galvin SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. *Nat Rev Microbiol* 2004; 2(1): 33-42.
14. Chakraborty H, Sen PK, Helms RW, Vernazza PL, Fiscus SA, Eron JJ, et al. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. *Aids* 2001; 15 (5): 621-627.
15. Baffi CW, Aban I, Willig JH, Agrawal M, Mugavero MJ, Bachmann LH. New syphilis cases and concurrent STI screening in a Southeastern U.S. HIV Clinic: A call to action. *Aids Patient Care STDs* 2010; 24 (1):23-29.
16. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS* 2004; 18(15):2075–79.
17. Palacios R, Jimenez-Onate F, Aguilar M, et al. Impact of syphilis infection on HIV viral load and CD4 cell counts in HIV-infected patients. *J Acquir Immune Defic Syndr* 2007; 44(3):356–59.
18. Kofoed K, Gerstoft J, Mathiesen LR, Benfield T. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: Influence on CD4 T-cell count, HIV-1 viral load, and treatment response. *Sex Transm Dis* 2006; 33(3):143–48.
19. Duffus WA, Mermin J, Bunnell R, et al. Chronic herpes simplex virus type-2 infection and HIV viral load. *Int J STD AIDS*. 2005; 16(11):733–35.



20. Rotchford K, Strum AW, Wilkinson D. Effect of coinfection with STDs and of STD treatment on HIV shedding in genital-tract secretions: systematic review and data synthesis. *Sex Transm Dis.* 2000;27(5):243–48
21. Sadiq ST, McSorley J, Copas AJ, et al. The effects of early syphilis on CD4 counts and HIV-1 RNA viral loads in blood and semen. *Sex Transm Infect* 2005; 81(5):380–85.
22. Poudel KC, Poudel-Tandukar K, Palmer PH, Mizoue T, Jimba M, Kobayashi J, et al. Coinfection of Sexually Transmitted Infections among HIV-Positive Individuals: Cross-Sectional Results of a Community-Based Positive Living with HIV (POLH) Study in Nepal. *J Int Assoc Provid AIDS Care.* 2015; 1–9.
23. Agmon-Levin N, Elbirt D, Asher I, Gradstein S, Werner B & Sthoeger Z. Syphilis and HIV co-infection in an Israeli HIV clinic: incidence. *Int J of STD & AIDS* 2010; 21 (4): 249-52.
24. Katusiime C, Schlech W F, Parkes-Ratanshi R, Sempa J, & Kambugu A. (2013). Characteristics of Sexually Transmitted Infections among High-Risk HIV-Positive Patients Attending an Urban Clinic in Uganda. *J Int Assoc Provid AIDS Care* 2013. 2016; 15(1):36-41.
25. Dang T, Jatton-Ogay K, Flepp M, Kovari H, Evison JM, Fehr J, et al. High prevalence of anorectal chlamydial infection in HIV-infected men who have sex with men in Switzerland. *Clin infect dis* 2009; 49(10), 1532-1535.
26. Grinsztejn B, Bastos FI, Veloso VG, Friedman RK, Pilotto JH, Schechter M, et al. Assessing sexually transmitted infections in a cohort of women living with HIV/AIDS, in Rio de Janeiro, Brazil. *Int J of STD & AIDS* 2006; 17(7), 473-78.
27. Mayer KH, O'Cleirigh C, Skeer M, Covahey C, Leidolf E, Vanderwarker R, et al. Which HIV-infected men who have sex with men in care are engaging in risky sex and acquiring sexually transmitted infections: findings from a Boston community health centre. *Sex Transm Infect* 2010; 86(1): 66 - 70.
28. Diaz A, Junquera M, Esteban V, Martínez B, Pueyo I, Suárez J, et al. HIV/STI co-infection among men who have sex with men in Spain. *Euro surveillance: bulletin*

Europeen sur les maladies transmissibles= European communicable disease bulletin.  
2008; 14(48):1424-7.

29. Asavapiriyant S, Lolekha R, Roongpisuthipong A, Wiratchai A, Kaoiean S, Suksripanich O, et al. Sexually transmitted infections among HIV-infected women in Thailand. BMC Public Health 2013; 13 (373): 1-12.
30. Romanowski B, Myziuk LN, Walmsley SL, Trottier S, Singh A E, Houston S, et al .Seroprevalence and risk factors for herpes simplex virus infection in a population of HIV-infected patients in Canada. Sex Transm Dis 2009, 36(3):165-9.
31. Leber A, MacPherson P, Lee BC. Epidemiology of Infectious Syphilis in Ottawa: Recurring Themes Revisited. Can J Public Health 2008; 99(5):401-5.
32. Case KK, Ghys PD, Gouws E, Eaton JW, Borquez A, Stover J, et al. Understanding the modes of transmission model of new HIV infection and its use in prevention planning. Bull World Health Organ 2012; 90(11):831-38A.
33. Saskatchewan Ministry of Health. Saskatchewan's HIV Strategy 2010 – 2014. Regina: Saskatchewan Ministry of Health; 2010. [Cited 2015 April 04]. Available from: <http://www.health.gov.sk.ca/hiv-strategy-2010-2014>.
34. Public Health Agency of Canada. Sexually Transmitted Infections—A Continued Public Health Concern. Ottawa: Public Health Agency of Canada; 2013. [Cited 2015 April 04]. Available from: <http://www.phac-aspc.gc.ca/cphorsphc-respcacsp/2013/sti-its-eng.php#figure-1>
35. Fee E, Krieger N. Understanding AIDS: historical interpretations and the limits of biomedical individualism. Am J Public Health. 1993; 83(10):1477-86.
36. Krieger N, Zierler S. What explains the public's health?--A call for epidemiologic theory. Epidemiology. 1996; 7(1):107-9.
37. Boerma JT, Weir SS. Integrating demographic and epidemiological approaches to research on HIV/AIDS: the proximate-determinants framework. Journal of Infectious Diseases. 2005; 191(Supplement 1):S61-7.

## **Chapter 2: Literature review**

This Chapter provides a brief background of HIV and AIDS. It describes the global epidemiology of HIV/AIDS. It also discusses epidemiology of HIV/AIDS in Canada, Saskatchewan and SHR. Finally, risk factors that may predict STIs acquisition among PLWH were discussed.

### **2.1 HIV/AIDS epidemiology**

Globally, over 60 million people are living with HIV and acquired immune deficiency syndrome (AIDS).(1-2) Among those affected it is estimated that 42% are females.(1-2) The global HIV prevalence was noted to be 0.8% amongst individuals between ages 15 to 49 years (3), with persons under the age of 25 years accounting for 25% of all new infections.(2) The infection has claimed about 25 million lives, making HIV/AIDS one of the most complex population health problems of the 21st century.(1) Most studies have identified the common mode of transmission of HIV as mother to child, blood transfusion, heterosexual, IDU and MSM.(2-5, 6) Although about 85% of HIV transmission globally is said to be via heterosexual transmission (2, 6, 7), for the purpose of this thesis, modes of transmission will include heterosexual, IDU, and MSM

Apart from the modes of transmission mentioned above other factors that could contribute to risk of HIV transmission include STI, age, gender, ethnicity, occupation, income, education, marital status, engagement in sex work, and migrants from endemic countries. (8 - 9)

#### **2.1.1 Canada**

In Canada, the number of HIV cases diagnosed between 2014 and 2015 has increased from 2,051 to 2,096.(10) Out of 2,096 HIV cases in 2015, 24.1% were women and 75.9% were men.(10) Annually, about 2,300-4,300 new cases of HIV infection occur in the nation.(9) In 2015, HIV diagnosed by age group had its highest increase amongst individuals between ages 25-29 and  $\geq$  50 years at 11.8% to 15.8% and 21.9% to 23.9% respectively.(10) Approximately 17.5% of Canada's HIV cases in 2015 was attributed to the Indigenous people.(10)

Transmission rate is said to vary in different exposure groups. In 2015, the highest prevalence of HIV infection amongst individuals  $\geq 15$  years old was attributed to MSM exposure category with 45.1%, followed by heterosexual (31.9%), IDU (16.3%). (10)

### ***2.1.2 Saskatchewan***

Although, the Canadian incidence rate of HIV has remained stable in the last decade (11-12), Saskatchewan has had a significant rise in the number of new cases of HIV since 2003. (13) In 2015, with a provincial average of 13.9/ 100,000, Saskatchewan had the highest incidence rates in the nation.(14) This rate was higher than that of Canada at 5.8/100,000.(14)

In the same year, 81% of HIV cases in Saskatchewan were from indigenous people. (14) The majority of HIV cases were reported in IDU (61%), followed by heterosexual contact (27%).(14) HIV cases in the province acquired via IDU exposure group ranged from 49% in 2014 to 79% in 2009.(14)

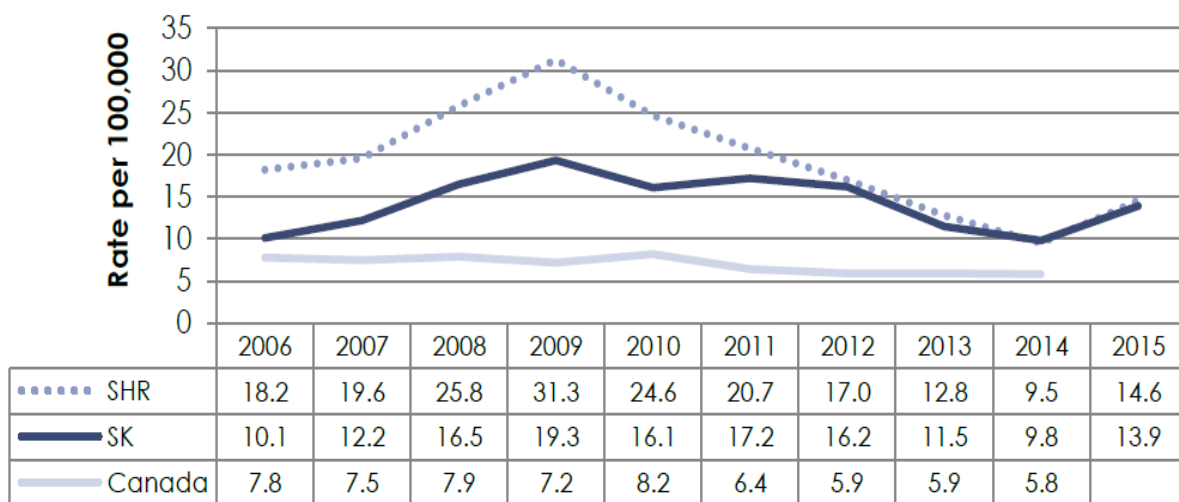
Apart from years 2005 and 2006, males account for most of the HIV cases in the province. (15) Sixty -two percent of 2015 HIV cases were males compared to 38% females.(14) The highest number of new HIV cases for Saskatchewan in year 2015 was found in SHR, followed by Prince Albert, and then Regina Qu'Appelle health region.(14)

### ***2.1.3 Saskatoon Health Region***

Saskatoon Health Region was not excluded from the epidemic and, recorded an incidence rate of 31.3 per 100,000 people in 2009, which was over four times that of the nation at that time. (4) see Figure 2.1 below. The region's HIV epidemic is also driven by the IDU population, accounting for about 66% of HIV infections between 2011 and 2015; this is followed by unsafe heterosexual sex. (4)

The region had 54% of all new cases of infection in the province in 2008. (16) This high proportion of newly diagnosed cases might be due to an intensive testing program in the health region. From 2011, HIV testing among the high-risk group has risen for both standard and point

of care testing at 28% and 12% respectively. (17) Sixteen percent of 600 newly diagnosed cases between 2006 and 2015 died as a result of the infection in SHR. (4)



**Figure 2.1: HIV rates per 100,000 Population, Saskatoon Health Region, Saskatchewan, and Canada, 2006 to 2015. (4)**

## 2.2. Risk factors predicting STIs acquisition among people living with HIV

Few publications were identified which examined the acquisition of STIs in PLWH. This literature review will not attempt to provide a detailed description of the impact of each risk factor on acquisition of STI among PLWH. Rather, it will provide an overview of the impact of the risk factors, where one exists. The review will draw correlation between the association of some of the risk factors with HIV acquisition and that of acquiring other STIs in PLWH. This is because more studies have been done in the area of HIV transmission. Furthermore, STIs, HIV inclusive are acquired via similar exposure channels. High-risk sexual behavior plays a major role in the transmission of both HIV and other STIs. The review will focus on variables that are available from SHR health service data for exploration in this research. These include the demographic, behavioral, and socioeconomic variables. Details of these variables are available in the methodology section. Even though, the risk factors will be discussed separately in this review, it is worth noting that these risk groups are not mutually exclusive, an individual could

have more than 1 exposure group, resulting in an overlap in the modes of transmission. For instance, a person can be a sex worker (SW) and also engage in IDU.

### ***2.2.1 Demographic***

The demographic variables that will be discussed in this section focus on biological factors that cannot be modified or change. It is different from behavioral factors, which can be altered.

#### ***Gender***

Gender and sex are risk factors that play an important role in the outcome of various health issues (18-19) including diagnosis of STI in PLWH. Based on this, current health research usually explores these two variables.(18-19) Before 1970s, gender was not considered in health research analysis.(19) Even though these variables are now being explored in health research, researchers still lack fundamental understanding of sex or gender concepts and as a result these terms are used interchangeably or incorrectly.(18-19) While some disciplines such as social sciences are more familiar with these concepts, others such as biomedical and clinical health fields are not.(18) The two terms have been reported to impact the same health outcome differently, thus, their incorrect use will result in the development of inappropriate interventions and policy.(18)

In order to appropriately use these two terminologies in health research, researchers need to clearly understand these two constructs. (18-19) Krieger (2004) stated that “...our science will only be as clear and error-free as our thinking”. (19, p. 656) For better understanding of these concepts, it is of utmost importance to define them.

Johnson *et al.* (2009) defined sex as “a multidimensional biological construct that encompasses anatomy, physiology, genes, and hormones, which together affect how humans are labelled and treated in the world”.(18, p.3) For example, “sex” concept comes into play in HIV heterosexual transmission. The European Study Group on heterosexual transmission of HIV in 1992, reported that “male to female sexual transmission of HIV is more efficient than female to male transmission”. (20, p.7) This implies that females are at higher risk of HIV acquisition compared to males and this is due to the variation in their biological and physiological composition. Therefore, research based on the concept described above should use “sex” in its analysis and not “gender”.

Sex is mostly denoted by male or female binary in health research. (18) However, research related to sex chromosomes showed that apart from the popular XY (male) and XX (female)

chromosomes, there are other chromosomal variations. (18) These include XXY, XYY and XO, hence binary representation of sex could result in omission of essential information associated with the other genetic chromosomes. (18)

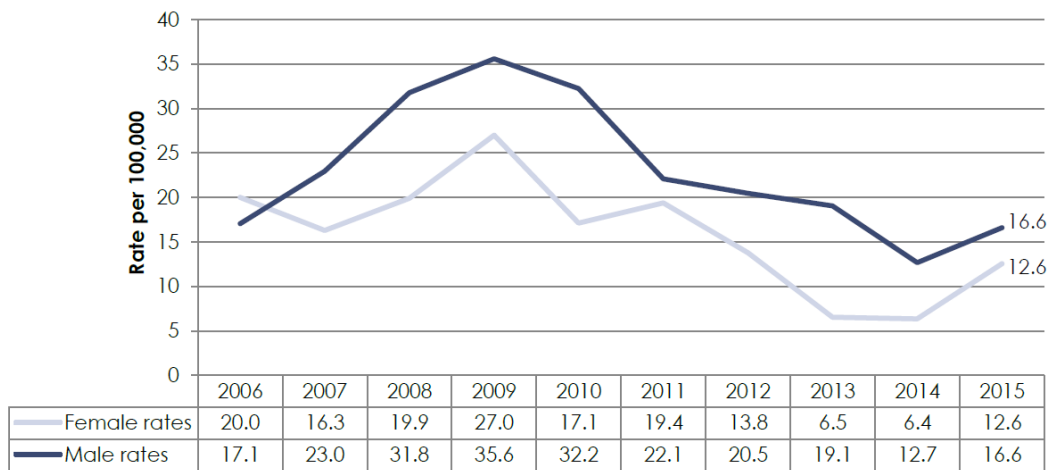
On the other hand, they defined gender as "...a multidimensional social construct that is culturally based and historically specific, and thus constantly changing. Gender refers to the socially prescribed and experienced dimensions of "femaleness" or "maleness" in a society, and is manifested at many levels".(18, p.3) Societal assessment of males to be superior over females shows a structure inequality.(18) The concept of gender is consistently associated with socioeconomic and political context on the population level and socioeconomic status at the individual level.(18) In HIV research, gender inequality due to socioeconomic status and cultural values was reported to have limit the ability of women to negotiate safe sex.(21- 22) Thus, increasing the risk of HIV acquisition amongst women as well as STIs acquisition.

Gender roles are usually determined socially and they arise from gendered experiences, cultural values and behavioral norms. (18) The societal conceptions with regard to men or women's behavior (dressing, mannerism and posture) will determine their gender roles. (18)

Although, sex and gender constructs differ, they are very connected and mutually impact one another.(18) For instance, an individual's secondary sex characteristics (penis/vagina) determine how they are addressed by the society.(18) This dictates their gender placement in the society as a man or woman or transgender.(18) At the same time, gender also influences sex.(18) Those men with high self-perception of masculinity and as such engage in high-risk sports notice a rise in their testosterone levels.(18) With this understanding, Prins *et al.*(2007) suggested "there is no difference in the use of the binary variables of sex and gender. The distinction between the two terms is usually relevant only when the mechanisms of influence are being studied". (23, p.107) The author reasons and agrees with Prins *et al.* Even though the health service data captured this variable using gender, the variable was denoted with male and female and not women and men.

Globally, male HIV rates are higher than that of the females as documented in section 2.1. The same trend has also been documented here in Canada with male HIV rates almost 3 times that of the females.(24) The province of Saskatchewan was reported to have the lowest male to female HIV ratio (3:2) in the whole of Canada.(25) In SHR, there was a rise in HIV rates for both males and females from 2006 to 2009, after which the rates started to drop, but since 2014 the rates are

increasing again, see Figure 2.2.(26) This graph shows that males were more affected than the females in SHR.



**Figure 2.2 : HIV rates per 100,000 populations by gender, Saskatoon Health Region, 2006 to 2015. (26)**

In contrast, some studies have recorded a disproportionate burden of infection among females.(21 - 22, 27) In the last five years, approximately half of all HIV infections worldwide have been diagnosed amongst women.(28) Women were reported to be economically dependent on their husbands and partners and as such having little or no control over their body and life (education and employment).(21-22) An Irish study showed there is an association between the rising HIV prevalence in women and their financial dependency on their sexual partners.(29) This impedes their ability to negotiate safe sex thus increasing the risk of acquiring HIV and other STIs.(5,22)

Some researchers have explored the role of gender inequality in some exposure groups, a major one being the IDU. Gender disparity in HIV prevalence among IDU was observed. (30-31) Globally, there is increasing concerns about the disproportionate burden of HIV among female IDUs. (30) Female IDU were reported to be more highly vulnerable to HIV infection than the male IDU.(30-31)

There are multiple reasons why females who inject drugs may be at higher risk of HIV infection compared to their male counterparts. (20) First and foremost, their male IDU sexual partners could introduce them to IDU. (32-33), This impairs their ability to negotiate protected sexual intercourse and risk for contracting HIV (32-33), this could also apply to acquisition of other



STIs. The iTrack study in Regina highlighted the role of risky sexual behaviors amongst IDUs in the transmission of HIV infection. (13) In their study, 88% of female participants had a regular sexual partner, however, 70% had never used a condom. (13) Also 24% of these group reported having casual sex partners, of which about 8% never used condom. (13)

In addition, female IDUs may also rely on their male sexual partners for drugs and injections, which increases their tendency to share drugs and needles. (30) Those who are not dependent on their male partners tend to engage in commercial sex work in order to sustain their drug habit. (34-35)

Another factor that could contribute to the risk of acquiring HIV amongst this group is sexual violence. (30) A Canadian study conducted in Vancouver documented a history of sexual violence among 68% of female IDUs compared to 19% among males. (30) This finding was reinforced by a Russian survey that showed that 21% of male IDUs abused their female IDU partners. (30)

Lastly, there is the high tendency for female IDUs to have male sexual partner who are also IDUs.(20) According to the European Study Group on heterosexual transmission of HIV in 1992, “male to female sexual transmission of HIV is more efficient than female to male transmission”.(20, p.7) This increases the risk of acquiring HIV amongst female IDUs via heterosexual contact.(20) We can assume that the role of gender in HIV transmission will be similar to that in acquiring other STIs in PLWH.

The available studies on STIs acquisition in PLWH have varying opinions on which gender is more affected. A systematic review carried out by Kalichman and colleagues in 2011, reported similarities in the prevalence of STIs in HIV-infected men and women, at 13.6% and 15.8% respectively.(6) On the other hand, several studies recorded that men living with HIV are more at risk of acquiring STI.(36- 38) Baffi *et al.*(2010) reported that men living with HIV are 2.5 times more likely to have other STIs than women.(38) This was supported by Manning *et al.* (2007) who observed that HIV-infected men are 1.5 times more at risk of having STI than women.(36)

The question with regards to which gender is more affected with the burden of STIs in PLWH has been inconclusive. This thesis will attempt to shed more light on this in the analysis.

## ***Age***

Age as a biological risk factor impacts several health outcomes (39), thus it will be important to discuss its role in acquiring other STIs in PLWH. Age here, will be referred to as age at diagnosis. It has been noted that older persons have a higher tendency to poor health status. (39) Older people living with HIV are reported to be more at risk of an expedited HIV progression. (39-43) HIV depresses their immunity and makes them more susceptible to several opportunistic infections (42), therefore increasing their risk of contracting STIs. The relationship between aging and HIV advancement is not gender specific (43), that is both males and female are affected. It also cuts across various exposure groups such as heterosexuals, MSM, and IDU. (43)

The association between age and acquiring other STIs in HIV-infected persons vary from one study to another. Asavapiriyant *et al.* (2013) reported individuals over 25 years as having higher STIs prevalence as opposed to those less than 25 years. (44) This finding has been supported by various other studies. (37, 45) Hu and colleagues came up with likely reasons that could be responsible for this increase among older ages. (37) These include inconsistent use of condom, increase in patronizing sex workers, and low uptake of STIs testing. (37)

On the contrary, Manning *et al.* (2007) observed that HIV-infected persons under 25 are 3.7 times more likely than those over 25 years to have STIs. (36) This association was also supported by several other studies. (38, 46)

Despite the fact that the age group of PLWH with other STIs was not clearly defined in studies, the author thinks its impact as a biological risk factor cannot be overlooked.

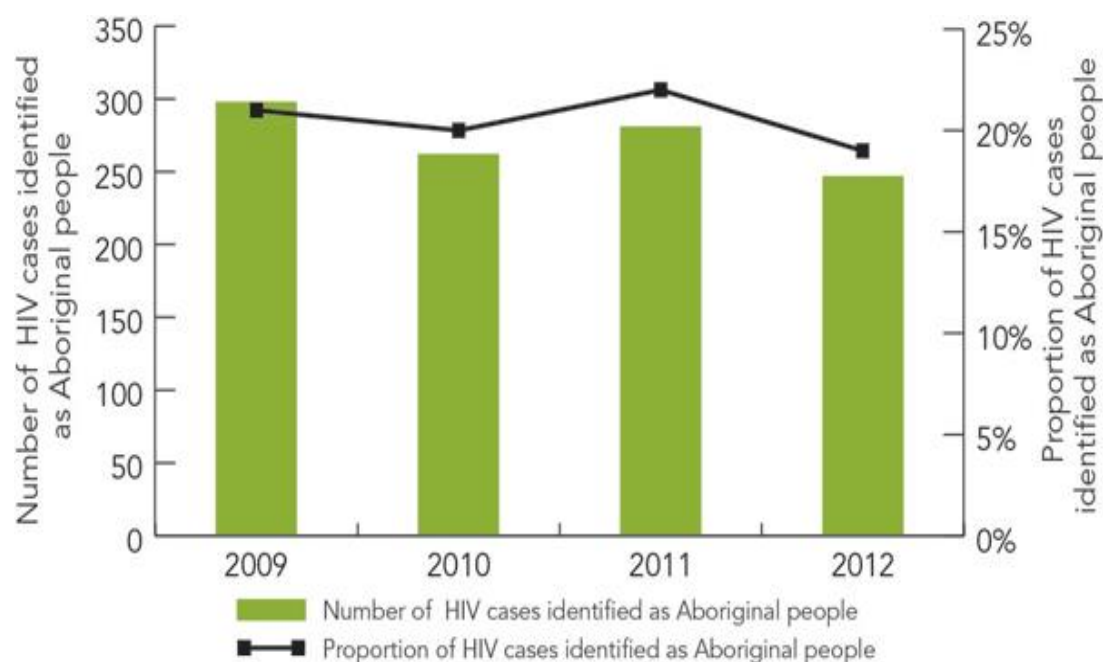
## ***Ethnicity***

The impact of ethnicity, cultural values and norms cannot be underestimated on health outcomes. This is because of the health disparities that have been observed among ethnic minorities in developed countries. (30) In North America, ethnic minorities are disproportionately affected by HIV and are also more at risk of acquiring the infection. (47-48) This finding was confirmed by various studies in USA. (49-52)

This work will focus its ethnicity discussion on Indigenous people because approximately 70% of clients in the SHR health service data used for this research are of First Nations' ancestry. I will also be drawing corollary from other ethnic minorities from other studies.

Indigenous peoples' health has been an area of concern for health sectors in many countries.(53) This is due to the low life expectancy experienced by this population, which results from chronic diseases, infectious diseases, and limited access to preventive and curative health services.(53) It is important to know that physical availability of health services to this group is not enough to address their health needs, rather, services that are culturally appropriate.(53) Other factors that may contribute to Indigenous peoples' poor health status include poverty, lack of education, poor physical and social environment, and substance abuse.(53-54) All of the aforementioned factors increase their susceptibility to being infected with STIs.(53)

Unfortunately, the burden of HIV infection has increased over the years among the Indigenous people in Canada, from about 1% in 1990 to 10.8% in 1999. (55) As at 2011, 8.9% of all PLWH are Indigenous people and the incidence rate in this population the same year was 12.2%, despite the fact that this group of people are only 4.3% of Canadian population (54), see Figure 2.3 below. The infection disproportionately affects males and youth aged 15-29 years.(54) HIV rate among Canadian Indigenous people has been reported to be higher than those in other countries such as New Zealand and Australia.(54) In 2011, IDU and heterosexual exposure accounts for the highest incidence of HIV infections among Indigenous people , with 58% and 30.2% respectively.(54) In view of this, the prevalence of STIs among HIV-infected Indigenous people may be on the high side, especially because these two exposures play a significant role in the transmission of HIV and other STIs.



**Figure 2.3 : Number and percentage of Aboriginal people\* among positive HIV tests 2009 to 2012 (\*Data from BC, AB, SK, MB, NS, NB, ON, PEI, NL, NU, NT and YT). (54)**

Finding from two Canadian studies among IDU reported an increase in HIV prevalence and incidence among Indigenous as compares to non- indigenous people.(53, 55) Studies in United States of America observed increase STIs among blacks living with HIV as compared to other ethnic group.(38, 46) Baffi *et al.* (2010) reported that HIV-infected ethnic minorities are 2.2 times more at risk of STIs than Caucasians.(38) Another American study showed 92.5% of HIV-infected blacks had other STIs.(46) This implies that attention should be paid to health needs of ethnic minorities, in our case, Indigenous population.

Even though, research on this topic with relation to Indigenous people are limited, we can draw corollary from the above discussion.

### **2.2.2. Behavioral factors**

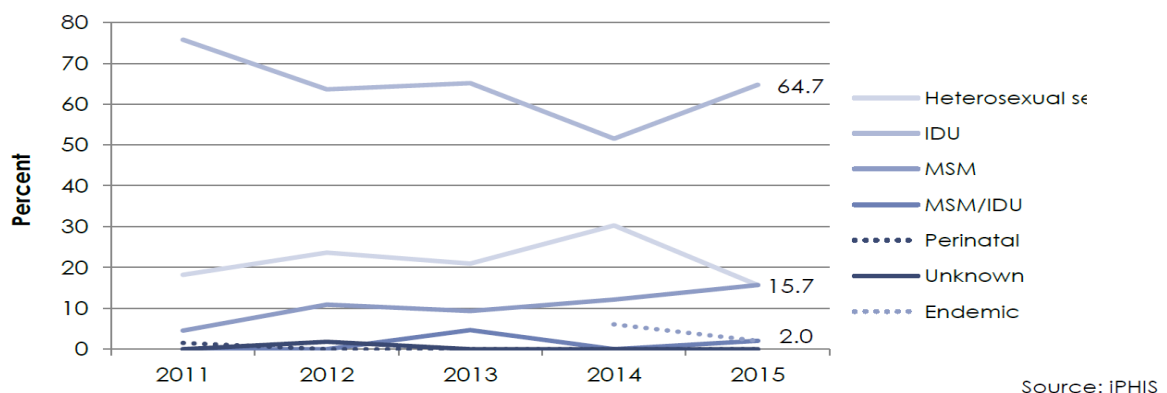
#### ***Intravenous drug use***

Globally, approximately 15.9 million persons are engaged in IDU out of which 3 million people live with HIV. (56-59) Also, about 5 -10% of HIV infection worldwide can be attributed to use of intravenous drug. (57-58) In the last few decades, the route of HIV transmission was noted to

have transitioned from sexual exposure to illicit drug use, especially IDU. (53) About 25% of HIV transmission in North America is linked to IDU.(53)

In Canada, an estimated 112,900 persons are involved with IDU.(3) With approximately 13.7% of all new HIV infections resulting from IDU and about 20% of all HIV infection in Canada arising from IDU population.(3, 59) This number was reported to have declined gradually in the last two decades.(3) It is worth knowing that majority of the IDU population in Canada are of the Indigenous people ethnicity.(3) Amongst women in Canada, about 23% of new HIV cases are due to IDU, which almost doubled that of the nation.(59)

As mentioned previously the HIV epidemic in Saskatchewan is driven by IDU exposure risk, this is followed by the heterosexual exposure.(13, 15) Out of 128 HIV cases acquired via IDU in 2010, 80 were males and 48 females.(15) Even though the percentage of IDU contributing to HIV transmission in SHR has decreased from about 75% in 2011 to 64.7% in 2015 (see Figure 2.4), the number is still high when compared to the national average of 13.7% in 2011.(3-4)



**Figure 2.4: Primary HIV transmission risk trend, Saskatoon Health Region, 2011 to 2015.**  
(4)

However, in recent years, various studies have shown the overlap in transmission mode between unsafe IDU and sexual behavior. (60) Locally, recent increase in sexually acquired HIV, in the face of high IDU, might be pointing to an overlap in the drivers of HIV transmission in the SHR.

Illicit drug use is usually associated with risky sexual behavior, and thus increasing the possibility of transmission of any sexually transmitted disease.(60) It has also been described as a

potential modifier of decision-making.(61) The use of these drugs impair proper decision making ability which results in various risky sexual behavior such as unprotected sex, having sex with multiple and casual partners.(61) Bachmann *et al.* (2005) concluded in their study that there was an association between illicit drug use and sexual risk behavior among PLWH (61), this serves as an indicator of their risk of acquiring other STIs. On this note, studies exploring this association had reported a high prevalence of STIs amongst HIV-infected IDUs. (61-62)

It is disappointing to see that the rate of HIV infection acquired via IDU remains on the rise, despite adequate HIV preventive strategies (including needle exchange programs (NEP)). (64) Surprisingly, the success of NEP is still controversial in some parts of the world despite the fact that quite a number of scientific papers have established its efficacy. (30, 57-58)

One factor that could be responsible for this is the continued needle sharing behavior.(29, 63) In 1988, Vancouver began one of the biggest NEP combined with a street nursing program.(29, 57) Although HIV prevalence was stable initially, there was an increase in 1994.(29, 57) Another study reported that about forty percent of IDUs still engage in needle sharing activities despite availability of NEP.(29) This was reinforced by a Vancouver study which reported that IDUs that attended NEP frequently usually become HIV positive.(57) Another factor reported to contribute to the rise in HIV prevalence amongst IDUs is inadequate NEP coverage.(57-58) Even though NEP is available in 82 countries, with these countries harbouring about 80% of the worlds IDUs, yet the HIV prevalence are still high in most of these nations because of inadequate NEP coverage.(57-58)

Several studies have indicated IDUs as high-risk group that expedites the transmission of HIV infection to groups with low risk. (33) This transmission was noted to be mostly via engagement in high risk behavior which includes both sexual and needle exchange. (33). The Canadian iTrack study showed that about 50% of the IDU population in Regina inject with sex partners (13), which increases the tendency to share needles.

HIV epidemic driven by IDUs is not as simple as it appears. Rather it may be an overlapping epidemic between the heterosexual and IDU group driven by complex network of high-risk behavior and sexual contact. (30, 33). These high-risk behavior and sexual contact plays an important role in the acquisition of other STIs among PLWH.

### ***Men Having Sex with Men***

Several studies amongst MSM reported that there is usually a high tendency to acquire HIV in a person with STIs. (64-65) The prevalence of STIs among HIV-infected MSM was documented to be high. (45, 66), due to their regular engagement in unprotected anal intercourse with casual and multiple partners. (45, 65), A study conducted by Mayer *et al.* in 2012, revealed a high prevalence of STIs amongst MSM living with HIV, with 87% coinfection as compared to the other modes of exposure.(65) Manning and his colleagues (2007) observed that the odds of HIV-infected MSM acquiring other STIs was twice that of heterosexuals.(36) These findings were supported by several other studies.(30, 45-46, 65) The practice of unprotected insertive and receptive anal intercourse among MSM with resultant bruising of the anal canal, has facilitated the transmission of STIs in this group.(65)

Various studies did report the rectal region as harboring asymptomatic gonorrhea and chlamydia infections (7, 65–67) and when left untreated serves as a transmission medium for both HIV and other STIs. (65) Acquisition of STIs among MSM living with HIV cannot be dealt with, without mentioning the effect of the use of illicit drugs. HIV infected MSM, who also have other STIs tend to use illicit drug (65), the association between the two was supported by several other studies. (68-69). Drug use potentiates high risk sexual behavior and decreases medication adherence, thereby increasing the infectiousness of these persons. (65)

Diaz and his colleagues (2009), in their study, recorded that almost half of HIV-infected MSM with STIs diagnosis had casual partners and only about 12% had a steady partner. (45) It is fascinating to know that despite been aware of their positive HIV status, MSM continue to engage in risky sexual behavior (45), thereby increasing the rate of being infected with other STIs. A high prevalence of STIs in MSM living with HIV as compared to those without STIs was reported by several studies in Australia (70), Germany (71), and the USA. (72)

Acquiring other STIs in PLWH was noted to disproportionally affect males, particularly MSM. (38, 45) This may be attributed to an increase in high-risk sexual behavior engaged in by MSM. In a study conducted by Sprenger *et al.* (2014) they reported that approximately 70% of MSM had over 2 or more sexual partners in the last 12 months.(73) However, 21.5% of heterosexual men and 10.7% women had over 2 or more sexual partners in the last 12 months.(73) They also observed that MSMs had a higher tendency to have casual sexual partners alone or casual and

regular partners.(73) These high-risk sexual behavior being practised by HIV- infected MSM may predispose them to the risk of acquiring STIs.

### ***Sex worker***

It is crucial to know that most research work reflecting the relationship between sex work (SW) and acquisition of STIs in PLWH was focussed on women and rarely on men. Sex workers can be defined as individuals who exchange sex for money or drugs due to their low socio-economic status.(74) Cohan *et al.* faulted this definition in their study.(75) Cohan and his colleagues felt the restriction of sex exchange to money and drugs alone can lead to misclassification of women who exchange sex for other valuables as non-sex workers.(75) They assumed that misclassification of some women in their study based on the first definition might have led into the distortion in association between the presence of STIs in PLWH and female sex worker.(75) The response rate in research involving SW are usually low because of stigma associated with the profession, thus most research carried out amongst this group make use of snowball sampling and convenient samples from STI clinics.(75)

Women engaged in sex work are usually involved in various high-risk sexual behavior, which makes them a key population in the acquisition and transmission of STIs.(44, 75-76) A study based in the USA reported a significant association between SW and having STIs in HIV-infected persons, documenting that HIV-infected participants with other STIs are almost 3 times more likely to be engaged in SW than those without STI.(46) In a study carried out among MSM, being a sex worker was associated with the risk of acquiring both HIV and STI.(45) Similar observation was noted in other studies.(7-78)

Injection drug use was also documented by several studies as popular among these women. (75-76) Some of the studies recorded the prevalence of IDU in SW to be 58% in Yunnan, China (79), 51% in seven United States cities (80), 56% and 65% in Vancouver and Montreal, Canada, respectively (81-82), 71% in Glasgow, Scotland (83), and 82% in Amsterdam, Netherlands. (74)

It is worth knowing that SW financial dependency on their clients in many instances predispose them to have little or no control over their body. (76) As such, they may be unable to negotiate condom use and use of intravenous drugs. (76) They may also be subjected to sexual violence from their customers, sexual or injection partners, hotel managers, and police. (76) These factors increase their risk of acquiring STIs.



### ***Heterosexual***

In the last few years the incidence of STI has risen significantly among heterosexual PLWH in high income countries. (66) This increase may be due to a rise in unsafe sexual practices, which exposes them to being infected by STIs. (66) In a study among commercial sex worker in Amsterdam, 30% of their participant tested positive for HIV. (74) The majority of these HIV positive participants self -identified as heterosexual and only one person was an IDU. (74) Des Jarlais *et al.* (2014) found an increase in HIV prevalence from 8% to 16% between 1995 to 1999 and 2005 to 2011 in a US study.(84) This study was conducted amongst non-injecting drug users and 95% of this group were heterosexuals.(84) They also found a higher prevalence of herpes simplex virus 2 among PLWH compared to those without HIV.(84) Another US study among PLWHA reported that about 43% of 207 PLWHA diagnosed with chlamydia practised heterosexual sex , while 38% were MSM.(36) On the contrary, a Netherlands study amongst 245 heterosexual HIV patients recorded only 1.6% of their participants with other STIs .(85) The findings in these studies might be due to the level of high risk sexual behaviour among this population. The higher the level of high risk behaviour, the higher the risk of HIV or other STIs transmission. (36,74,84,85)

In SHR, transmission risk among heterosexual persons was reported to have increased from 13% in 2009 to 20.9% in 2013. (86) A health region report in 2015 showed an increase of 36% in HIV cases from 2014 to 2015, attributing the rise to sexual transmission. (63) Again, an increase in sexual HIV transmission will reflect increased risk of STI transmission.

### ***Sex with confirmed /suspected PLWH***

The act of having sex with individuals that have laboratory diagnosis of HIV or suspected to have HIV, due to the presence of some clinical features, was categorised as one of the high-risk sexual behavior.(44, 46, 66) Hague *et al.* (2011) mentioned that the diagnosis of STIs in PLWH implies ongoing sexual risk behavior after being diagnosed with HIV.(46) They found an increase in STIs amongst African-Americans living with HIV; these participants were MSM less than 25 years.(46) This increase was attributable to their high-risk sexual behavior after been diagnosed with HIV and other STIs.(46) Mayer *et al.* seconded this finding.(65)

### ***2.2.3. Socioeconomic factors***

The majority of HIV and other STIs preventive programs are targeted at individual level behavioral changes, while the role of social and economic factors in STIs transmission at the population level is being totally ignored.(87) Social inequalities in health have been well established in Canada(90), with various studies reporting a significant association between socioeconomic status (SES) of an individual and their health outcomes.(89-90) This association was observed all over Canada, though it varies from one region to another. The Western regions (Prairies and British Columbia) “premature mortality gaps according to a Deprivation Index” was higher than that in other regions. (88, p.470) Socioeconomic factors have also been noted to be essential in explaining infectious disease pattern and an association was observed between HIV infection and social and material deprivation. (91) HIV is described as a disease of marginalized and impoverished people or nations. (91)

In recent times, health status is assessed objectively and subjectively using clinical indicators. (92) A good example of an approach of assessing health subjectively is the use of health-related quality of life (HRQOL), which is associated with the socioeconomic contextual factors that affect human health.(92)

Ruiz Perez *et al.* (2004), in their study among PLWH, noted a significant association between socioeconomic factors (being employed, social support) and better physical and mental health status. (92) It is worth noting that mental status of an individual impacts their decision-making ability, which subsequently affects their engagement in high risk sexual behavior as previously discussed in Section 2.3.2. Several studies have characterized SES using education, income and employment as its proxy measure (87,93), but some others consider gender inequality as one of the proxy measures. (94) Saskatoon Health Region uses the Deprivation Index as a proxy measure of SES. This index will be discussed in detail in the methodology section of Chapter 3.

#### ***Employment/Income***

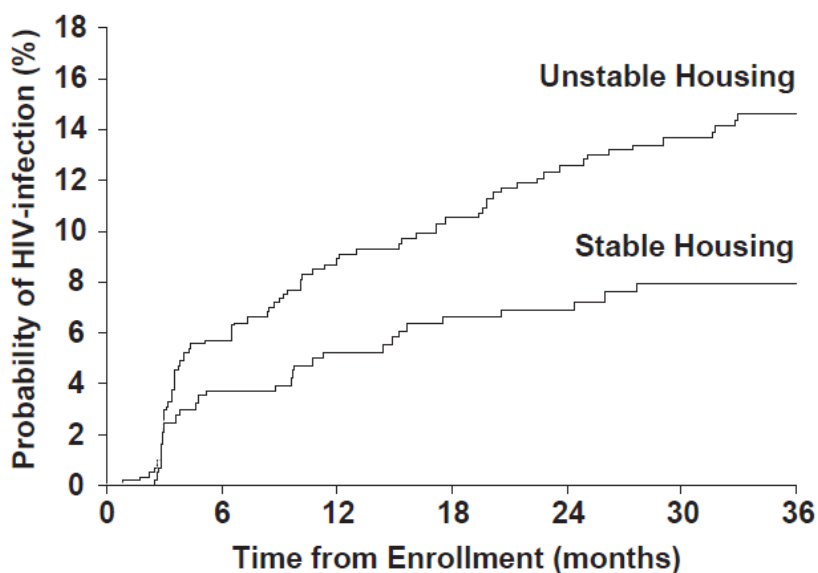
Unemployment has been identified as a predictor of both morbidity and mortality in human society.(95) Having a job plays a primary role in the sustenance of income level and availability of housing, particularly among individuals with chronic diseases such as HIV.(95) Previous studies on unemployment rates among PLWH recorded the rate as ranged from 45% to 65%.(96-101) Unemployment in this study was reported to affect females, older age, individuals with low

education, immigrants, and IDU.(94) Dray-Spira *et al.* (2007) found that the employment rate was 75% higher among the general population compared to PLWH before 1994 and 91% higher after 1994.(95) Unemployment was recorded more among persons with low education.(95)

Shortly before the year 2000, low SES was reported by a review of Canadian evidence as a relevant predictor in the rise in HIV death having controlled for age, disease stage and, access to health care.(87) This discovery was backed up by a British Columbia study, early in 2000's (93), this study measured SES using neighbourhood income.(93) Their finding was associated to inequitable access to triple ART, which was available to high SES.(93) The role of SES in the transmission of HIV has been viewed from severally angles, having different factors implicated.

Employment plays a primary role in the availability of stable housing. The effect of unstable housing on the transmission of HIV was widely underscored and should not be overlooked. Living condition was classified by World Health Organization as a pivotal health determinant.(102) With this in mind several studies were carried out to determine the relationship between poor housing condition and unfavourable health outcomes.(102) The majority of these studies identified a significant association between these two variables.(103-105) A Canadian study among young homeless women found that these women are 10 times more likely to die when compared to other women in the general population.(102)

In HIV research, unstable housing condition was related to high-risk behavior such as IDU, this subsequently leads to risky sexual behaviors (102), predisposing these individuals to HIV and other STIs. Corneil and colleagues (2004), in a study conducted in Vancouver among IDUs, found unstable housing was related to several HIV risk behavior such as sharing of needles and sex trade. (102) Their analysis found a significant increase in HIV rate in individuals who live in unstable housing (see Figure 2.5). (102)



**Figure 2.5: Cumulative probability of HIV infection among IDU stratified by housing status at baseline. (102)**

In most instances women are more likely to be categorised in the low SES globally. (22) Some of them were observed to engage in sex trade due to their low SES. (22) Most studies documented that their financial disempowerment could have resulted from low or no education and unemployment. (27) Considering the fact that these women are economically dependent on their clients and partners, their opinion on safe sexual practice is usually disregarded (22- 27, 9496), and this increases their risk of acquiring HV and other STIs. (22)

Some other studies reported that low SES indirectly impacts the transmission of HIV through inadequate nutrition and micronutrients.(106, -107) The likelihood of poor nutrition among PLWH was attributed to their poor financial status.(106, -107) Certain factors that were suspected to have played a role in the malnourishment observed in PLWH include IDU, alcohol use, inadequate financial resource to sustain necessary dietary requirement, progression of the disease, and side effect from the use of ART.(106) Though the study could not say for sure if the poor nutritional state was independently from each of these factors or whether it was more of a collective effect of all of them.(106)

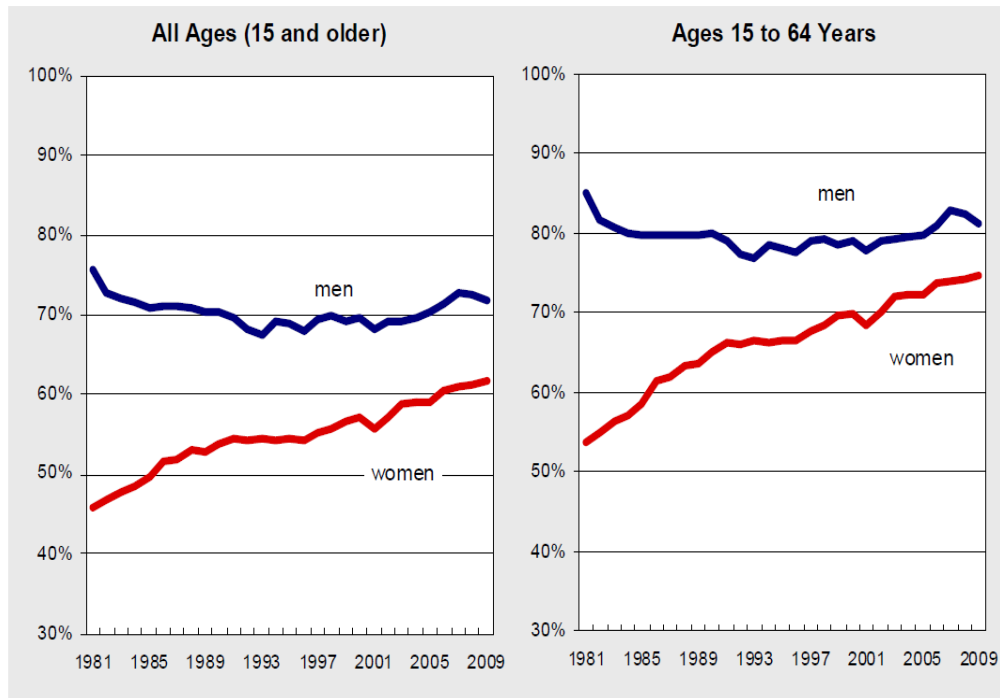
In the presence of poor nutrition and low micronutrient intake the immune system is impaired and vagina epithelium is also damaged, thereby increasing the risk of heterosexual HIV

transmission. (94, 107-108) Transmission of STI might also increase as a result of heterosexual exposure and secondly through breakdown in vagina epithelium. A study reported a higher life expectancy in HIV-infected individuals with better SES, presumably due to adequate nutritional intake which improves with high SES. (107)

### ***Education***

A study conducted in Spain reported that PLWH with no or low education are 3.4 times more likely to acquire other STIs as compares to those with high education level.(45) Zhu *et al.* (2011) seconded the findings when they recorded that the odds of persons with lower education acquiring HIV and other STIs was 7.4 times more than for individual with higher education.(109) Having reflected on the effect of low SES in HIV and other STIs transmission, gender inequality might be contributing to their association, no wonder it is considered as one of the proxy measure of SES.(94)

Taking a peep into Saskatchewan's women status in terms of income, employment and education, they might not be left out of gender inequality when compared to the male counterpart. (110) Figure 2.6 illustrate employment rate of males and females from 1981 and 2009 in Saskatchewan. (110) It is obvious from the graph that the males are more employed compared to females. More women in Saskatchewan earn between \$10/hour to \$19.99/hour, while men are paid over \$20/hour (110), this could result into inequality in income.



**Figure 2.6: Employment rates in Saskatchewan by sex and age group, 1981 to 2009. (110)**

Even though, more females were reported to have attended university, as evidence by the graduation rate (62%) for first degree in 2008 (113), women's education is still limited to certain courses.(112) The number of females admitted to some university programs such as architecture and engineering is very limited.(111-112) Seventy- eight percent of graduates from these programs were males in 2008.(111) The high rate for male graduates was also noticed in mathematics, computer and information sciences programs, having 70% of graduates to be males.(111)

This literature review can not draw a clear conclusion regarding the variables explored in this Chapter. Hopefully, the next 2 Chapters will be able to shed light on the relationship between these variables and acquisition of STIs in PLWH.

## 2.3 References

1. Gao X, Wu Y, Zhang Y, Zhang N, Tang J, Qiu J, Lin X, Du Y. Effectiveness of School-based Education on HIV/AIDS Knowledge, Attitude, and Behavior among Secondary School Students in Wuhan, China. PLoS One. 2012; 7(9): e4881.
2. Simon V, Ho DD, Karim QA. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. The Lancet. 2006; 368(9534):489-504.
3. Public Health Agency of Canada. HIV/AIDS Epi Updates: National HIV Prevalence and Incidence Estimates for 2011. Ottawa: Public Health Agency of Canada; 2014. [Cited 2015 May 04]. Available from <http://www.phac-aspc.gc.ca/aids-sida/publication/epi/2010/1-eng.php>.
4. Saskatoon Health Region. Bloodborne Infection – Human Immunodeficiency Virus (HIV). Saskatoon: Saskatoon Health Region; 2014. [Cited 2017 June 04]. Available from: [http://www.communityview.ca/pdfs/2016\\_shr\\_series4\\_bloodborne\\_hiv.pdf](http://www.communityview.ca/pdfs/2016_shr_series4_bloodborne_hiv.pdf)
5. Morison L. The global epidemiology of HIV/AIDS. Br Med Bull. 2001; 58 (1): 7-18.
6. Kalichman SC, Pellowski J, Turner C. Prevalence of sexually transmitted co-infections in people living with HIV/AIDS: systematic review with implications for using HIV treatments for prevention. Sex Transm Infect 2011, 87 (3):183-90.
7. Romanowski B, Myziuk LN, Walmsley SL, Trottier S, Singh A E, Houston S, et al. Seroprevalence and risk factors for herpes simplex virus infection in a population of HIV-infected patients in Canada. Sex Transm Dis 2009, 36(3):165-9.
8. Becker ML, Kasper K, Pindera C, Cheang M, Rodger D, Sanche S, et al. Characterizing the HIV epidemic in the prairie provinces. Can J Infect Dis Med Microbiol 2012; 23 (1):19-22.
9. Belvedere LM, Miller CL, Hogg RS. Shifting Sands: Changing Regional and Gender-specific Patterns of HIV/AIDS Mortality in Canada, 1987 to 2008. Can J Public Health. 2012; 103 (3):202-6.
10. Public Health Agency of Canada. HIV in Canada : surveillance summary tables, 2014-2015. [Cited 2017 August 02]. Available from: <https://www.canada.ca/en/public->

health/services/publications/diseases-conditions/hiv-in-canada-surveillance-summary-tables-2014-2015.html?wbdisable=true

11. Public Health Agency of Canada. HIV and AIDS in Canada. Surveillance Report to December 31, 2009. Surveillance and Risk Assessment Division, Centre for Communicable Diseases and Infection Control. 2010. [Cited 2015 December 15]. Available from: <http://www.phac-aspc.gc.ca/aids-sida/publication/survreport/2013/dec/index-eng.php>.
12. Disease Prevention Unit, Population Health Branch, Saskatchewan Ministry of Health. HIV and AIDS in Saskatchewan 2010. 2011 November 30, 2011. [Cited 2015 December 16]. Available from: [https://www.google.ca/webhp?sourceid=chrome-instant&rlz=1C1CAFA\\_enCA632CA649&ion=1&espy=2&ie=UTF-8#q=Disease+Prevention+Unit%2C+Population+Health+Branch%2C+Saskatchewan+Ministry+of+Health.+HIV+and+AIDS+in+Saskatchewan+2010.+2011+November+30%2C+2011](https://www.google.ca/webhp?sourceid=chrome-instant&rlz=1C1CAFA_enCA632CA649&ion=1&espy=2&ie=UTF-8#q=Disease+Prevention+Unit%2C+Population+Health+Branch%2C+Saskatchewan+Ministry+of+Health.+HIV+and+AIDS+in+Saskatchewan+2010.+2011+November+30%2C+2011).
13. Saskatchewan Ministry of Health. Saskatchewan's HIV Strategy 2010 – 2014. Regina: Saskatchewan Ministry of Health; 2010. [Cited 2015 December 15]. Available from: <http://www.health.gov.sk.ca/hiv-strategy-2010-2014>.
14. Saskatchewan Ministry of Health. HIV Prevention and control program report for 2015. Regina: Saskatchewan Ministry of Health; 2015. [Cited 2017 August 02]. Available from: <https://www.saskatchewan.ca/government/government-structure/ministries/health/other-reports/annual-report-archive#step-4>
15. Saskatchewan Ministry of Health. HIV and AIDS in Saskatchewan 2010. Regina: Saskatchewan Ministry of Health; 2011. [Cited 2015 December 18]. Available from <https://www.saskatchewan.ca/government/government-structure/ministries/health/other-reports/annual-report-archive#step-4.b>.
16. Lemstra M, Rogers M, Thompson A, Moraros J, Buckingham R. Risk indicators associated with injection drug use in the Indigenous people population. AIDS Care. 2012; 24 (11):1416-1424.



17. Saskatoon Health Region. Bloodborne and Sexually Transmitted Infections. Saskatoon: Saskatoon Health Region; 2014. [Cited 2015 December 17]. Available from: [https://www.saskatoonhealthregion.ca/locations\\_services/Services/Health-Observatory/Documents/Reports-Publications/2014\\_shr\\_series4\\_hsrfull.pdf](https://www.saskatoonhealthregion.ca/locations_services/Services/Health-Observatory/Documents/Reports-Publications/2014_shr_series4_hsrfull.pdf)
18. Johnson J, Greaves L, Repta R. Better science with sex and gender: Facilitating the use of a sex and gender-based analysis in health research. *Int J Equity Health*. 2009; 8(1):14.
19. Krieger N. Genders, sexes, and health: what are the connections--and why does it matter? *Int J Epidemiol*. 2003; 32(4):652-7.
20. Des Jarlais DC, Boltaevb A, Feelemyera J, Bramsona H, Arasteha K, Benjamin W. et al . Gender disparities in HIV infection among persons who inject drugs in Central Asia: A systematic review and meta-analysis. *Drug and Alcohol Dependence* 2013; 132: S7– S12.
21. Carovano K. More than mothers and whores: redefining the AIDS prevention needs of women. *International Journal of Health Services* 1991; 21(1):131-42.
22. Dean H D, Fenton KA. Addressing social determinants of health in the prevention and control of HIV/AIDS, viral hepatitis, sexually transmitted infections, and tuberculosis. *Public Health Rep*. 2010; 125(4):1-5.
23. Prins MH, Smits KM, Smits LJ: Methodologic ramifications of paying attention to sex and gender differences in clinical research. *Gend Med*. 2007; 4 Suppl B: S106-10.
24. Public Health Agency of Canada. Executive Summary - Report on Sexually Transmitted Infections in Canada: 2011. (. Ottawa: Public Health Agency of Canada; 2014 Aug. [Cited 2015 December 10]. Available from: [www.phac-aspc.gc.ca/sti-its-surv-epi/index-eng.php](http://www.phac-aspc.gc.ca/sti-its-surv-epi/index-eng.php).
25. HIV and AIDS in Canada. Surveillance Report to December 31, 2008. Ottawa, Ontario: Surveillance and Risk Assessment Division, Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada; 2009.
26. Saskatoon Health Region. HIV Rates by Gender and Age Group Saskatoon Health Region, 2011 to 2015. Saskatoon: Saskatoon Health Region; 2014. [Cited 2017 June 21]. Available from:

[http://www.communityview.ca/pdfs/2016\\_shr\\_series4\\_bloodborne\\_hiv\\_additionaldata.pdf](http://www.communityview.ca/pdfs/2016_shr_series4_bloodborne_hiv_additionaldata.pdf)

27. Buvé A, Kizito B, Mutangadura G. "The spread and effect of HIV-1 infection in sub-Saharan Africa." *The Lancet*. 2002 Jun; 359(9322): 2011-17.
28. United Nations Population Fund. *State of World Population: the promise of equality*. New York: United Nations Population Fund; 2005. [Cited 2015 December 17]. Available from: <http://www.unfpa.org/publications/state-world-population-2005>.
29. Clarke S, Keenan E, Bergin C, Lyons F, Hopkins S, Mulcahy F. The changing epidemiology of HIV infection in injecting drug users in Dublin, Ireland. *HIV Medicine* 2001; 2(4):236-40
30. Des Jarlais DC, Feelemyer JP, Modi SN, Arasteh K, Hagan H. Are females who inject drugs at higher risk for HIV infection than males who inject drugs: an international systematic review of high seroprevalence areas? *Drug Alcohol Depend*. 2012; 124(1):95-107.
31. European Monitoring Centre for Drugs and Drug Addiction. *Annual Report: the state of drug problem in Europe*. Belgium: European Monitoring Centre for Drugs and Drug Addiction; 2006. [Cited 2015 December 17]. Available from: <http://www.entakd.lt/en/files/2006-annual-rep-en.pdf>
32. Magnus M, Kuo I, Phillips G, Rawls A, Peterson J, Montanez L, et al. Differing HIV Risks and Prevention Needs among Men and Women Injection Drug Users (IDU) in the District of Columbia. *J of Urban Health: Bulletin of the New York Academy of Medicine* 2012; 90 (1):157-66.
33. Volz E, Frost SD, Rothenberg R, Meyers LA. Epidemiological bridging by injection drug use drives an early HIV epidemic. *Epidemics* 2010; 2(3):155-64.
34. Benotsch EG, Somlai AM, Pinkerton SD, Kelly JA, Ostrovski D, Gore-Felton C. et al. Drug use and sexual risk behaviors among female Russian IDUs who exchange sex for money or drugs. *Int J STD AIDS* 2004; 15(5):343-7.

35. Cleland CM, Des Jarlais DC, Perlis TE, Stimson G, Poznyak V. HIV risk behaviors among female IDUs in developing and transitional countries. *BMC Public Health* 2007; 7(1):271
36. Manning SE, Pfeiffer MR, Nash D, Blank S, Sackoff J, Schillinger J. Incident Sexually transmitted infections among Persons Living with Diagnosed HIV/AIDS in New York City, 2001–2002: A Population-Based Assessment. *Sex Transm Dis*, 2007; 34 (12):1008–15.
37. Hu QH, Xu JJ, Zou HC, Liu J, Zhang J, Ding HB, et al. Risk factors associated with prevalent and incident syphilis among an HIV-infected cohort in Northeast China. *BMC infectious diseases*. 2014; 14(1):658.
38. Baffi CW, Aban I, Willig JH, Agrawal M, Mugavero MJ, Bachmann LH. New syphilis cases and concurrent STI screening in a Southeastern U.S. HIV Clinic: A call to action. *Aids Patient Care STDs* 2010; 24 (1):23-9.
39. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med* .2006 Sep 19; 145(6):397-406.
40. McCune JM. The dynamics of CD4 T-cell depletion in HIV disease. *Nature* 2001; 410 (6831):974-79.
41. Mocroft A, Gill MJ, Davidson W, Phillips AN. Are There Gender Differences in Starting Protease Inhibitors, HAART, and Disease Progression Despite Equal Access to Care? *JAIDS J Acquired Immune Defic Syndromes* 2000; 24 (5):475-82.
42. Phillips AN, Lee CA, Elford J, Webster A, Janossy G, Timms A, et al. More rapid progression to AIDS in older HIV-infected people: the role of CD4 T-cell counts. *J Acquir Immune Defic Syndr* 1991; 4(10):970-5.
43. Pezzotti P, Phillips AN, Dorrucci M, Lepri AC, Galai N, Vlahov D, et al. Category of exposure to HIV and age in the progression to AIDS: longitudinal study of 1199 people with known dates of seroconversion. *BMJ* 1996; 313(7057):583-86.

44. Asavapiriyant S, Lolekha R, Roongpisuthipong A, Wiratchai A, Kaoiean S, Suksripanich O, et al. Sexually transmitted infections among HIV-infected women in Thailand. *BMC Public Health* 2013; 13 (373): 1-12.
45. Diaz A, Junquera M, Esteban V, Martínez B, Pueyo I, Suárez J, et al. HIV/STI co-infection among men who have sex with men in Spain. *Euro surveillance: bulletin European sur les maladies transmissibles= European communicable disease bulletin*. 2008; 14(48):1424-7.
46. Hague JC, Muvva R, Miazad RM. STD coinfection and reinfection following HIV diagnosis: Evidence of continued sexual risk behavior. *Sex Transm Dis* 2011; 38 (4):347-8.
47. U.S. National Institute of Allergy and Infectious Diseases. NIAID Fact Sheet. HIV infection in minority populations. 2005 Apr. [cited 2015 December 18]. Available from: <http://www.thebody.com/content/esp/art6559.html>. Retrieved December 18 2015
48. Rothenberg R, Woelfel M, Stoneburner R, Milberg J, Parker R, Truman B. Survival with the acquired immunodeficiency syndrome. Experience with 5833 cases in New York City. *The New England Journal of Medicine*. 1987; 317(21):1297-302.
49. Lee LL, MKaron J, Selik R, Neal JJ, Fleming PL. Survival after AIDS diagnosis in adolescent and adults during the treatment era, United States, 1984-1997. *Journal of the American Medical Association*. 2001; 285(10):1308-15.
50. Grigoryan A, Hall HI, Durant T, Wei X. Late HIV diagnosis and determinants of progression to AIDS or death after HIV diagnosis among injection drug users, 33 US States, 1996-2004. *PLoS ONE*. 2009; 4(2):e4445.
51. Hall HI, McDavid K, Ling Q, Sloggett A. Determinants of progression to AIDS or death after HIV diagnosis, United States, 1996 to 2001. *Annals of Epidemiology*. 2006; 16(11):824-33.
52. Hall HI, Byers RH, Ling Q, Espinoza L. Racial/ethnic and age disparities in HIV prevalence and disease progression among men who have sex with men in the United States. *American Journal of Public Health*. 2007; 97 (6):1060-6.

53. Wood E, Montaner JS, Li K, Zhang R, Barney L, Strathdee SA, et al. Burden of HIV infection among Indigenous people injection drug users in Vancouver, British Columbia. *Am J Public Health*. 2008 Mar; 98(3):515-19.
54. Public Health Agency of Canada. HIV/AIDS among Indigenous people People in Canada. Ottawa: Public Health Agency of Canada; 2014. [Cited 2015 December 19]. Available from: <http://www.phac-aspc.gc.ca/aids-sida/publication/epi/2010/8-eng.php#a2>.
55. Kevin Craib KJ, Spittal PM, Wood E, Laliberte N, Hogg RS, Li K, et al. Risk factors for elevated HIV incidence among Indigenous people injection drug users in Vancouver. *CMAJ* 2003 Jan 7; 168 (1):19-24.
56. Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet*. 2008; 372(9651):1733-45.
57. Hyshka E, Strathdee S, Wood E, Kerr T. Needle Exchange and the HIV Epidemic in Vancouver: Lessons Learned from 15 years of research. *Int J Drug Policy*. 2012; 23(4): 261–270.
58. Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick RP. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. *Lancet*. 2010; 375(9719):1014-28.
59. CATIE. The epidemiology of HIV in people who inject drugs in Canada. Toronto: Ontario; 2015. [Cited 2015 December 02]. Available from: <http://www.catie.ca/fact-sheets/epidemiology/injection-drug-use-and-hiv-canada>.
60. Des Jarlais DC, Arasteh K, McKnight C, Hagan H, Perlman DC, Semaan S. Associations between herpes simplex virus type 2 and HCV With HIV among injecting drug users in New York City: the current importance of sexual transmission of HIV. *Am J Public Health*. 2011; 101(7):1277-83.
61. Bachmann LH, Grimley DM, Waithaka Y, Desmond R, Saag MS, Hook EW. Sexually Transmitted Disease/HIV Transmission Risk Behaviors and Sexually Transmitted Disease Prevalence among HIV-Positive Men Receiving Continuing Care. *Sex Transm Dis*, 2005; 32 (1):20–6.

62. Trecker MA, Dillon JA, Lloyd K, Hennink M, Waldner CL. Demographic and behavioural characteristics predict bacterial STI reinfection and coinfection among a cross-sectional sample of laboratory-confirmed gonorrhea cases in a local health region from Saskatchewan, Canada. *Can J Public Health*. 2015; 106 (2):17-21.
63. Canadian Broadcasting Corporation News. HIV cases increase 36% in Saskatoon Health Region. Saskatoon: Saskatchewan; 2015. [Cited 2015 December 02]. Available from: <http://www.cbc.ca/news/canada/saskatoon/hiv-cases-increase-36-in-saskatoon-health-region-1.3345229>
64. Blocker ME, Levine WC, St. Louis ME. HIV prevalence in patients with syphilis, United States. *Sex Transm Dis* 2000 ; 27 (1): 53-59.
65. Mayer KH, Bush T, Henry K, Overton ET, Hammer J, Richardson J, et al. Ongoing sexually transmitted disease acquisition and risk-taking behavior among US HIV-infected patients in primary care: implications for prevention interventions. *Sex Transm Dis* 2012; 39 (1):1-7.
66. Desquilbeta L, Deveau C, Goujardb C, Huberta JB, Derouineauc J, Meyera L, et al. Increase in at-risk sexual behavior among HIV-1- infected patients followed in the French PRIMOCohort. *AIDS* 2002; 16(17): 2329–33.
67. Leber A, MacPherson P, Lee BC. Epidemiology of Infectious Syphilis in Ottawa: Recurring Themes Revisited. *Can J Public Health* 2008; 99(5):401-5.
68. Mansergh G, Flores S, Koblin B, et al. Alcohol and drug use in the context of anal sex and other factors associated with sexually transmitted infections: Results from a multi-city study of highrisk men who have sex with men in the USA. *Sex Transm Infect* 2008; 84(6):509-11.
69. Drumright LN, Little SJ, Strathdee SA, et al. Unprotected anal intercourse and substance use among men who have sex with men with recent HIV infection. *J Acquir Immun Defic Syndr* 2006; 4 43(3):344-50.
70. Jin F, Prestage GP, Zablotska I, Rawstorne P, Kippax SC, and Donovan B, et al. High rates of sexually transmitted infections in HIV positive homosexual men: data from two community based cohorts. *Sex Transm Infect*. 2007; 83 (5):397-9.

71. Dudareva-Vizule S, Haar K, Sailer A, Wisplinghoff H, Wisplinghoff F, Marcus U, et al. Prevalence of pharyngeal and rectal Chlamydia trachomatis and Neisseria gonorrhoeae infections among men who have sex with men in Germany. *Sex Transm Infect.* 2014; 90(1):46-51.
72. Whittington WL, Collis T, Dithmer-Schreck D, Handsfield HH, Shalit P, Wood RW, et al. Sexually transmitted diseases and human immunodeficiency virus-discordant partnerships among men who have sex with men. *Clin Infect Dis.* 2002; 35(8):1010-17.
73. Sprenger K, Evison JM, Zwahlen M, Vogt CM, Elzi MV, Hauser C, et al. Sexually transmitted infections in HIV-infected people in Switzerland: cross-sectional study. *PeerJ* 2014; 2:e537.
74. van den Hoek JA , van Haastrecht HJ, Scheeringa-Troost B, Goudsmit J, Coutinho RA. HIV infection and STD in drug addicted prostitutes in Amsterdam: potential for heterosexual HIV transmission. *Genitourin Med,* 1989; 65(3):146- 150.
75. Cohan DL, Kim A, Ruiz J, Morrow S, Reardon J, Lynch M, et al. Health indicators among low income women who report a history of sex work: the population based Northern California young women's survey. *Sex Transm Infect* 2005; 81(5):428-33.
76. Strathdee SA, Lozada R, Martinez G, Vera A, Rusch M, Nguyen L, et al. Social and structural factors associated with HIV infection among female sex workers who inject drugs in the Mexico-US border region. *PLoS One.* 2011; 6 (4):e19048.
77. Williamson LM, Dodds JP, Mercey DE, Hart GJ, Johnson AM. Sexual risk behaviour and knowledge of HIV status among community samples of gay men in the UK. *AIDS.* 2008 May 31; 22(9):1063-70.
78. Bellis MA, Cook P, Clark P, Syed Q, Hoskins A. Re-emerging syphilis in gay men: a case-control study of behavioural risk factors and HIV status. *J Epidemiol Community Health.* 2002; 56(3):235-236.
79. Chen XS, Yin YP, Liang GJ, Gong XD, Li HS, Pomeroy G, et al. Sexually transmitted infections among female sex workers in Yunnan, China. *AIDS Patient Care STDS.* 2005; 19(12):853-860.

80. Cohen JB, Wafsy C, Gill P, Aguilar S, Witte J, Bigler W, Sikes RK, Leonard T, French J, Massey J. Antibody to human immunodeficiency virus in female prostitutes. *MMWR. Morbidity and mortality weekly report*. 1987; 36(11):157-61.
81. Shannon K, Kerr T, Bright V, Gibson K, Tyndall MW. Drug sharing with clients as a risk marker for increased violence and sexual and drug-related harms among survival sex workers. *AIDS Care*. 2008; 20(2):228-34.
82. Weber AE, Boivin JF, Blais L, Haley N, Roy E. HIV risk profile and prostitution among female street youths. *J Urban Health*. 2002; 79 (4):525-35.
83. McKeganey N, Barnard M, Leyland A, Coote I, Follet E. Female street working prostitution and HIV infection in Glasgow. *BMJ*. 1992 3; 305(6857):801-04.
84. Des Jarlais DC, McKnight C, Arasteh K, Feelemyer J, Perlman DC, Hagan H, et al. A perfect storm: crack cocaine, HSV-2, and HIV among non-injecting drug users in New York City. *Substance use & misuse*. 2014;49(7):783-92..
85. Heiligenberg M, van der Loeff MFS, de Vries HJ, Speksnijder AG, Geerlings SE, Coutinho R, et al. Low prevalence of asymptomatic sexually transmitted infections in HIV-infected heterosexuals visiting an HIV clinic in the Netherlands. *AIDS*. 2012;26(5):646-9.
86. Saskatoon Health Region. Rates of HIV declining but more needs to be done. Saskatoon: Saskatoon Health Region; 2014. [Cited 2015 May 04]. Available from: [https://www.saskatoonhealthregion.ca/locations\\_services/Services/Health-Observatory/Documents/Reports-Publications/2014\\_shr\\_series5\\_hsrfull.pdf](https://www.saskatoonhealthregion.ca/locations_services/Services/Health-Observatory/Documents/Reports-Publications/2014_shr_series5_hsrfull.pdf)
87. Lurie P, Hintzen P, Lowe RA. Socioeconomic obstacles to HIV prevention and treatment in developing countries: the roles of the international monetary fund and the World Bank. *AIDS*. 1995; 9 (6):539-46.
88. Pampalon R, Hamel D, Gamache P. Health inequalities, deprivation, immigration and Indigenous people in Canada: a geographic perspective. *Can J Public Health*. 2010; 101(6):470-74.
89. Humphries KH, van Doorslaer E. Income-related health inequality in Canada. *Soc Sci Med*. 2000; 50(5):663-71.



90. James PD, Wilkins R, Detsky AS, Tugwell P, Manuel DG. Avoidable mortality by neighbourhood income in Canada: 25 years after the establishment of universal health insurance. *J Epidemiol Community Health*. 2007; 61(4):287-296.
91. Marí-Dell'Olmo M, Rodríguez-Sanz M, Garcia-Olalla P, Pasarín MI, Brugal MT, Caylà JA, Borrell C. Individual and community-level effects in the socioeconomic inequalities of AIDS-related mortality in an urban area of southern Europe. *J Epidemiol Community Health*. 2007; 61(3):232-40.
92. Ruiz Perez I, Rodriguez Baño J, Lopez Ruz MA, del Arco Jimenez A. Causse Prados M, Pasquau Liaño J, et al. Health - related quality of life of patient with HIV: impact of sociodemographic, clinical and psychosocial factors. *Qual Life Res*. 2005; 14(5):1301-10.
93. Wood E, Montaner JS, Chan K, Tyndall MW, Schechter MT, Bangsberg D, et al. Socioeconomic status, access to triple therapy, and survival from HIV-disease since 1996. *AIDS*. 2002; 16 (15): 2065-72.
94. Gillespie S, Kadiyala S, Greener R. Is poverty or wealth driving HIV transmission? *AIDS*. 2007; 21(7): 5-16.
95. Dray-Spira R, Gueguen A, Ravaud JF, Lert F. Socioeconomic differences in the impact of HIV infection on workforce participation in France in the era of highly active antiretroviral therapy. *Am J Public Health*. 2007; 97(3):552-58.
96. Cunningham WE, Andersen RM, Katz MH, Stein MD, Turner BJ, Crystal S, et al. The impact of competing subsistence needs and barriers on access to medical care for persons with human immunodeficiency virus receiving care in the United States. *Med Care*. 1999 ; 37(12):1270-81.
97. Dray-Spira R, Lert F, Marimoutou C, Bouhnik AD, Obadia Y. Socio-economic conditions, health status and employment among persons living with HIV/AIDS in France in 2001. *AIDS Care*. 2003; 15(6):739-48.
98. Ezzy D, de Visser R, Bartos M. Poverty, disease progression and employment among people living with HIV/AIDS in Australia. *AIDS Care*. 1999; 11(4):405-14.
99. Fleishman JA. Transitions in insurance and employment among people with HIV infection. *Inquiry*. 1998; 35(1):36-48.

100. Goldman DP, Bao Y. Effective HIV treatment and the employment of HIV (+) adults. *Health Serv Res.* 2004; 39(6 Pt 1):1691-12.
101. Rabkin JG, McElhiney M, Ferrando SJ, Van Gorp W, Lin SH. Predictors of employment of men with HIV/AIDS: a longitudinal study. *Psychosom Med.* 2004; 66(1):72-8.
102. Corneil TA, Kuyper LM, Shoveller J, Hogg RS, Li K, Spittal PM, et al. Unstable housing, associated risk behaviour, and increased risk for HIV infection among injection drug users. *Health Place* 2006; 12(1):79-85.
103. Riley ED, Wu AW, Perry S, Clark RA, Moss AR, Crane J, et al. Depression and drug use impact health status among marginally housed HIV-infected individuals. *AIDS Patient Care STDS.* 2003; 17(8):401-6.
104. Teesson M, Hodder T, Buhrich N. Alcohol and other drug use disorders among homeless people in Australia. *Subst Use Misuse.* 2003; 38(3-6):463-74.
105. Zlotnick C, Tam T, Robertson MJ. Disaffiliation, substance use, and exiting homelessness. *Subst Use Misuse.* 2003; 38 (3-6):577-99.
106. Perreault S. The incarceration of Indigenous people people in adult correctional services. Ottawa: Statistics Canada; 2009 Jul. [Cited 2015 Mar 16]. Available from: <http://www.statcan.gc.ca/pub/85-002-x/2009003/article/10903-eng.pdf>
107. Bärnighausen T, Hosegood V, Timaeus IM, Newell ML. The socioeconomic determinants of HIV incidence: evidence from a longitudinal, population-based study in rural South Africa. *AIDS.* 2007; 21(7): 29–38.
108. Paton NI, Sangeetha S, Earnest A, Bellamy R. The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy. *HIV Med.* 2006; 7(5):323-30.
109. Zhu BY, Bu J, Huang PY, Zhou ZG, Yin YP, Chen XS, et al. Epidemiology of sexually transmitted infections, HIV, and related high-risk behaviors among female sex workers in Guangxi Autonomous Region, China. *Jpn J Infect Dis* 2012; 65(1):75-8.
110. Saskatchewan Ministry of Social Services. Women in the Saskatchewan labour market: a comparison of wage rates. Regina: Saskatchewan Ministry of Social Services; 2010. [Cited

2015 April 02]. Available from: <http://www.saskapprenticeship.ca/wp-content/uploads/2012/07/2010-Women-in-the-Sask-Labour-Market.pdf>.

111. Status of Women Canada. Women in Canada at a glance: statistical highlights. Ottawa: Status of Women Canada; 2012. [Cited 2015 April 02]. Available from: <http://www.swc-cfc.gc.ca/rc-cr/stat/wic-fac-2012/glance-statistical-eng.pdf>.
112. Leger-Anderson A. Women and education. Regina: The Encyclopedia of Saskatchewan; 2006. [Cited 2015 Mar 30]. Available from: [http://esask.uregina.ca/entry/women\\_and\\_education.html](http://esask.uregina.ca/entry/women_and_education.html).

## **Chapter 3: Manuscript 1: Exploring risk factors for sexually transmitted infections in people living with HIV in Saskatoon Health Region**

### **3.1 Abstract**

**Background:** The diagnosis of other STIs in PLWH suggest the possibility that PLWH are putting non-infected individuals at risk of HIV infection. Thus, identification of subgroups of PLWH at risk of STI acquisition is essential to guide intervention programs, such as to prevent further transmission of HIV and other STIs. Studies exploring risk factors for STI acquisition in HIV are not available in SHR, and limited in Canada overall.

**Objective:** To explore whether either gender or IDU are risk factors for STI acquisition in the year before and after HIV diagnosis in SHR.

**Methods:** This study examined SHR health services data on PLWH during the years 2009 to 2014. Twenty-two PLWH with STIs diagnosis within a year before and after HIV diagnosis were compared to one hundred and thirty three PLWH without STI diagnosis for variables potentially associated with STI acquisition in HIV.

**Result:** There was a bivariate association between the potential risk factors, gender, age, sex worker, and MSM and the risk for STI acquisition in the year before and after HIV diagnosis in SHR, at p-value <0.20. Multivariable analysis showed an association with marginal statistical significance between female (OR: 4.99; CI: 0.89 -27.3) and the risk for STI acquisition in the year before and after HIV diagnosis in SHR. There was also a significant association between sex work (OR: 5.0; CI: 1.03 -24.6) and the risk for STI acquisition in PLWH during this period in SHR. No association was observed between IDU and the risk for STI acquisition in the year before and after HIV diagnosis in SHR (OR: 0.2; CI: 0.03 -1.2). No interaction was observed between the variables.

**Conclusion:** The acquisition of STI in HIV shows that PLWH continuously engage in high-risk behavior, even after HIV diagnosis. To prevent or reduce the acquisition of these STIs in HIV public health practitioners should carefully select programs to address these risky behaviors.

### **3.2 Introduction**

Studies have shown an increased risk of HIV transmission when the infection co-exists with other STIs, especially in the presence of inflammation and ulcer. (1-3) Even though coexistence between HIV and STIs is said to affect the risk of transmission of both diseases (4), much work has not been done on the possibility of acquiring STIs after an HIV infection as compared to the risk of acquiring HIV in a person with STI. The diagnosis of other STIs in PLWH suggest the possibility that PLWH are increasing the risk of HIV infection in non-infected individuals. (5) This calls for further preventive measures in this population, therefore identification of subgroups of PLWH at risk of acquiring other STIs is essential to guide intervention programs.(5)

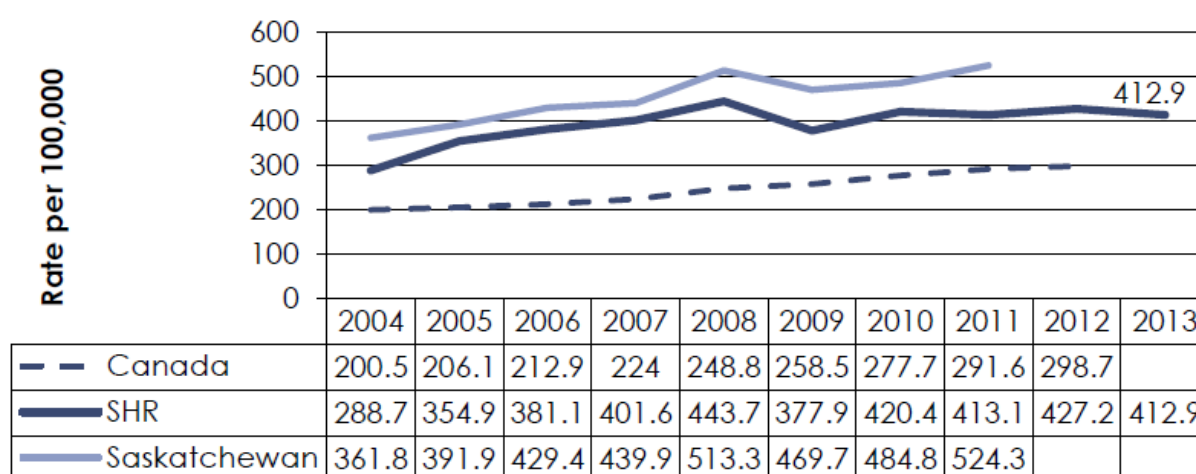
In SHR, data for HIV and other STIs are captured separately. Human immunodeficiency virus and other STIs coexistence data can only be made available when the region's HIV data is linked to that of other STIs. Hence, a separate overview on HIV and other STI with respect to gender and IDU will be provided in this section.

The most common reportable STI in Canada is chlamydia infection, followed by Neisseria gonorrhea, and syphilis infection.(6, 7) According to the Public Health Agency of Canada (PHAC), STI rates have increased over the years as seen in Table 3.1 below.(7) Chlamydia infection affects more women between 20-24 years, while gonorrhoea affects more men than women, aged 15-29 years.(6, 7)

**Table 3.1: Sexual transmitted infection rate over 10 years from 2002-2011. (7)**

Year	Chlamydia		Gonorrhea		Infectious Syphilis	
	Cases	Rates	Cases	Rates	Cases	Rates
2002	56,266	179.5	7,365	23.5	482	1.5
2010	93,329	273.7	10,743	31.5	1,698	5.0
2011	100,044	290.4	11,397	33.1	1,757	5.1

Sexually transmitted infections have also been on the rise in SHR.(8) Although the rates are dropping in the recent years, they are still high compared to the national average with chlamydia, gonorrhoea and syphilis having 412.9, 61.5, 1.2 per 100,000 respectively in 2013.(8) see Figure 3.1 for chlamydia rates in Canada, Saskatchewan, and SHR.



**Figure 3.1: Chlamydia rate per 100,000 populations, Saskatoon Health Region, Saskatchewan, and Canada, 2004 to 2013. (8)**

In SHR chlamydia infection is the most commonly reported STI, with the infection affecting more females than males. This is similar to the national chlamydia distribution.(8) The infection majorly affects young women ages 15 to 24 years and men, ages 20 to 29 years.(8) This is followed by gonococcal infection, which often co-infects with chlamydia.(8) Contrary to

chlamydial gender distribution, gonorrhea cases are almost the same for both males and females, although males are more likely to be symptomatic.(8) The age distribution for gonococcal infection is similar to that for chlamydia infection.(8) Saskatoon Health Region's syphilis rates were reported to be lower than both national and provincial rates.(8) The infection was noted to disproportionately affect more men than women, with the majority of the affected men being less than thirty years of age.(8) These infections were reported to be transmitted via unprotected sexual intercourse.(8) Discussion of the independent relationship of gender or IDU with HIV can be found in Section 2.1 (HIV/AIDS Epidemiology). More information can also be found in Sections 2.3.1 (Gender) and 2.3.2 (IDU).

It has been documented that the use of injection drugs is affiliated with risky sexual behavior, and subsequently the risk of acquiring STIs in an individual infected with HIV.(9) Injection drug use impairs decision making with regard to sexual behavior, hence, the increased tendency to acquire STI.(9, 10) With IDU contributing over 70% of HIV transmission in SHR (11), it is important to assess if this risk factor also contributes to the risk of acquiring other STIs in PLWH. Literature search did not reveal any studies exploring risk factors for acquiring STIs among PLWH in SHR. Studies examining this association were also limited in Canada. *Note that the risk for acquiring other STIs in HIV in our study implies risk factors for STI acquisition in the year before and after HIV diagnosis*. This study explored whether either gender or IDU are risk factors for STIs acquisition in the year before and after HIV diagnosis in SHR. Other STIs in this study were limited to chlamydia trachomatis, gonococcal infections, and syphilis.

### **3.3 Methods**

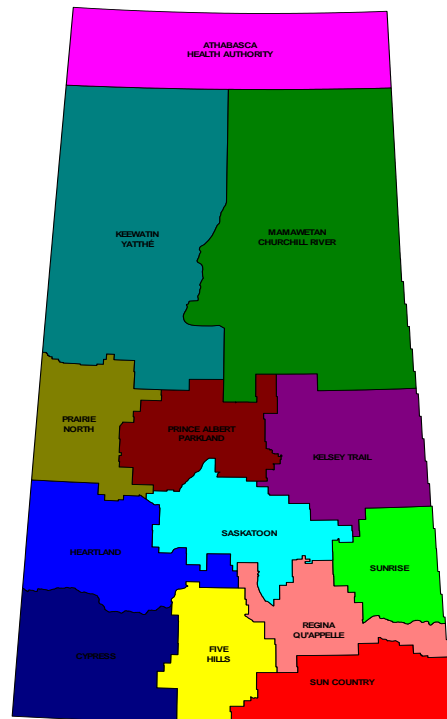
#### ***3.3.1 Study design***

Saskatoon Health Region health services data on PLWH during the years 2009 to 2014 was used for this study. HIV positive individuals with a record of other STIs and HIV positive individuals with no record of STIs were compared for variables potentially associated with STIs acquisition in PLWH.

#### ***3.3.2 Setting and population***

Saskatoon Health Region is situated in the central part of the province of Saskatchewan; see Figure 3.2 (12), and it is the largest health region in the province.(13) The region's population accounts for 30% of the province with approximately 350,000 people in 2014.(13) In 2011,

people of Indigenous people descent comprised of 10% of the health region's population, and 10% of the population were made up of other ethnic minorities.(14) The study population includes HIV-infected patients during the years 2009 to 2014 as recorded by the Public Health Observatory (PHO).



**Figure 3.2: Map of Saskatchewan (12)**

### ***3.3.3 Operational and ethics approval***

Ethics approval and Operational approval were obtained from the University of Saskatchewan Behavioral Research Ethics Board and SHR respectively.

### ***3.3.4 Data***

This public health dataset consisted of diagnosed HIV cases and individuals who tested positive for an STI. It reports positive laboratory results of reportable diseases notified by physicians to public health in SHR. Data collection was facilitated by the HIV case reporting form (See appendix A) .The HIV data were directly linked to other STIs using Personal health number



(PHN), while its linkage to deprivation quintile used encounter identification number. These data were retrieved from Integrated Public Health Information System (iPHIS).

### ***3.3.5 Inclusion and exclusion criteria***

All HIV positive cases reported to PHO from January 1, 2009 to August 15, 2014 were eligible to be included in the study. However, participants used for the analysis were limited to reported HIV-infected patients with and without other STIs in the year before and after HIV diagnosis. This study cohort was divided into two groups, the first group had STIs, while the second group did not. The time frame was used in order to equalize the opportunity for both groups to present with STIs. The time frame was also used because HIV and other reportable STI records do not follow patients when they move from one Regional Health Authority to another, and this could affect the accuracy for selecting controls for the study. HIV cases prior to 2009 were not used because they were reported non-nominally, without name or health services number identifier thus making it difficult to link to other nominally reported STIs. Inclusion and exclusion criteria are summarized below.

#### **Inclusion criteria:**

- (a) HIV positive patients with at least one other STI\* in the year before and after HIV diagnosis that were reported to PHO of SHR between 2009 and 2014.
- (b) HIV positive patients with no record of other STI\* either in the year before and after HIV diagnosis and outside this period that were reported to PHO of SHR between 2009 and 2014 .

#### **Exclusion criteria**

- (a) HIV cases reported prior to 2009 or after 2014.

**Note:** STI\*- newly reported chlamydia, gonorrhea, or syphilis.

### ***3.3.6 Variables***

These variables are mandated to be collected by the regions under the Public Health Act in Saskatchewan. See description of collected variables below.

**Gender** : This variable was obtained from the HIV case report form and laboratory results detailing STI diagnosis. In the case report it was recorded as male, female and others. The first two options were frequently selected and will be used in this analysis.

**Age at diagnosis** : This was calculated by subtracting patient date of birth recorded in either the HIV case reporting form or STI laboratory result, from the date of HIV diagnosis. Age in this data set ranges from 18 -73 years, this was grouped into 3 categories: <30 years, 30-39 years and  $\geq 40$  years.

**Ethnicity** : The variable was collected from the HIV case reporting form. This variable is made up of several ethnicities (see appendix B), which were self-declared. However, it was re-categorised into Indigenous people and non- Indigenous people because of the limited data set.

**HIV Exposures Categories** : Risk factors for HIV transmission were obtained from the HIV case reporting form. In Canada, primary exposure risk for HIV is assigned to an individual with multiple risks. This shows the most likely route of transmission. Primary risk uses a hierarchy of risk to assign probable exposure category, with the aid of ranking (see Appendix C for complete list of all exposure categories , their interpretation, and ranking). These exposure risk were self-reported.

**Deprivation Quintile** : A Deprivation Index (DI) is a tool used to monitor socio-economic inequalities in health.(15) Deprivation quintile was used as a proxy for income and education level in this study. The index was derived from the postal code, making use of the total national Deprivation Index.(15) The index has been available since 1991(16), but the most generally used version in Canada was developed in Québec in 1999.(15) This has been used in Québec for the last 10 years.(15) The Deprivation Index was developed using data from 2006 census and robust statistical methods.(15, 16) The DI has two components, the material and social components, which are combined to calculate the overall Deprivation Score (Total deprivation).(15, 16) See Figure 3.3 below.

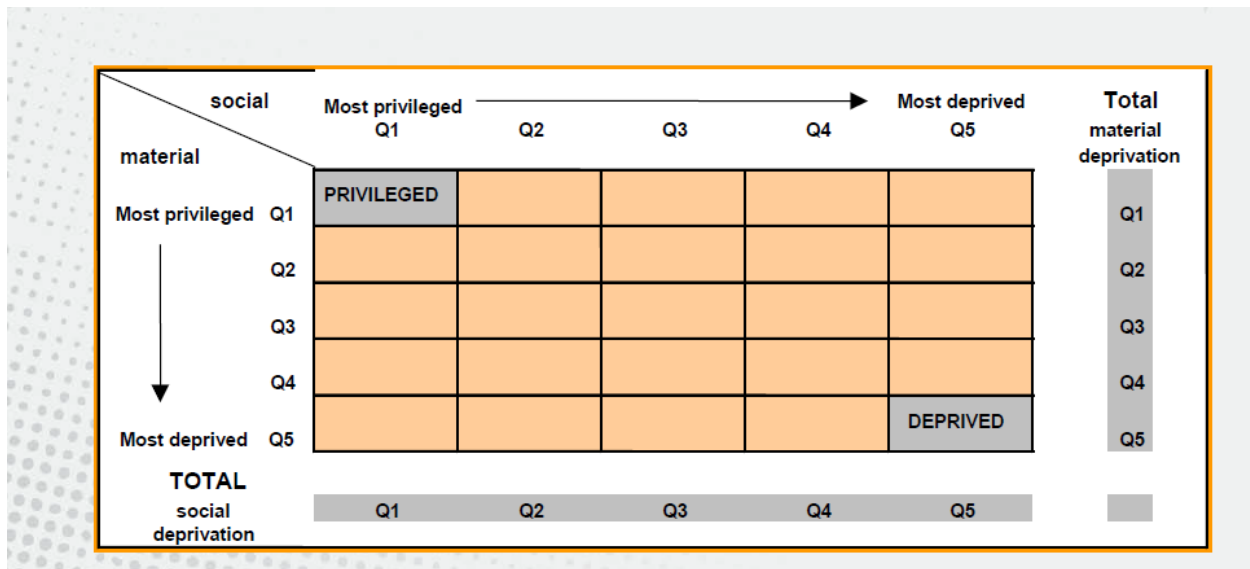
The variables included in the material component of the Deprivation Index are:

- The proportion of people aged 15 years and older with no high school diploma
- The employment to population ratio of people aged 15 years and older

- The average income of people aged 15 years and older

The variables included in the social component of the Deprivation Index are:

- The proportion of individuals aged 15 years and older living alone
- The proportion of individuals aged 15 years and older who are separated, divorced or widowed
- The proportion of single-parent families



**Figure 3.3: Combining material and social deprivation quintiles into total deprivation. (15)**

Where Quintile 1 (Q1) is the most affluent quintile and Quintile 5 (Q5) is the least affluent quintile.

“The Deprivation Index is calculated at the dissemination area (DA) level. The DA is the lowest geographic area, for which census data are available.(16) It is made up of one or more adjacent dissemination blocks (16), and its population ranges between 400 -700 people.(15) Principal Component Analysis for each dissemination area is used to determine the factor scores using social and material components.(15) The DA are then ranked according to their factor scores and designated to a quintile.(16) Note that in SHR, approximately 20% of the population was covered.(16) Scantly populated DAs were not classified.(16) Other DAs not classified include

those with high volume of collective households or institutionalized persons and those established on First Nations reserves.(16)

The PHO tagged these variables in their data set as:

- QMATLOC = local material deprivation quintile
- QSOCLOC = local social quintile
- TOTDEPLOC = total local (combination of material and social scores) (16).

The quantiles were re-categorised into Not-deprived (Q1-Q3) and Deprived (Q4-Q5), because of the limited data set.

### ***3.3.7 Variable selection***

The independent variables available for analysis were summarized in Table 3.2 below. However, not all of these variables were considered for the study analysis for a number of reasons. Marital status was not explored because it was 85% incomplete. Number of sexual contacts was also excluded from the analysis because the contact database does not contain a unique identifier, which allows direct linkage of HIV data to contact data. The contact database also does not have enough nominal identifiers to make a probabilistic link. Lastly, immigrant status was not included in the analysis because only one HIV-infected participants without STIs was documented. Again, it is worth noting that cases of previously reported HIV, diagnosed in another country, other provinces in Canada or Regional Health Authority, were not reported as new cases of HIV in SHR.

### ***3.3.8 Dependent variables***

The dependent variable of interest was a dichotomous indicator of acquisition of other STIs in the year before and after HIV diagnosis (Yes/No).

**Table 3.2: Variables available in database**

Category	Variable	Description	Type
Demographics	Gender Age Ethnicity	Female, Male or Other At Diagnosis White, First Nations, Métis, African, Asian, Other	Categorical Continuous Categorical
HIV Risk Factors	Heterosexual, Heterosexual sex with IVdruguser, Heterosexual sex with bisexual male, Heterosexual sex with person from endemic country, Born in endemic country, if yes, which country, Heterosexual sex with person with HIV/AIDS (diagnosed or suspected),Injection non-prescription drug user, Received blood or blood components after 1985, Occupational exposure,Other medical	Category of HIV Exposure	Categorical

	exposure, Other non-medical exposure (tattoo, acupuncture), Mother-to-child- transmission Sex Trade Worker, Sex with a partner of the same sex,		
Deprivation Quantile	Material deprivation quantiles (QMATLOC) Social deprivation, quantiles(QSOCLOC), Total deprivation quantiles (TOTDEPLOC)	Categories of deprivation quantiles	Categorical
Encounter Date	Date	Date of first encounter	Continuous

Variables were chosen after considering their potential influence in the risk for acquisition of STIs in PLWH from literature review. Table 3.3 below shows the variables used in our analysis.

**Table 3.3: Variables used in the statistical analysis**

Category	Variable	Description	Type
Demographics	Gender	Female, Male or Other	Categorical
	Age	At Diagnosis	Categorical
	Ethnicity	White, First Nations, Métis, African, Asian, Other	Categorical
HIV Risk Factors	Heterosexual, Heterosexual sex with person with HIV/AIDS (diagnosed or suspected), Injection non-prescription drug user, Sex Trade Worker, Sex with a partner of the same sex,	Category of HIV Exposure	Categorical
Deprivation Quantile	Material deprivation quantiles (QMATLOC) Social deprivation, quantiles(QSOCLOC), Total deprivation quantiles (TOTDEPLOC)	Categories of deprivation quantiles	Categorical

### **3.3.9 Data Analysis**

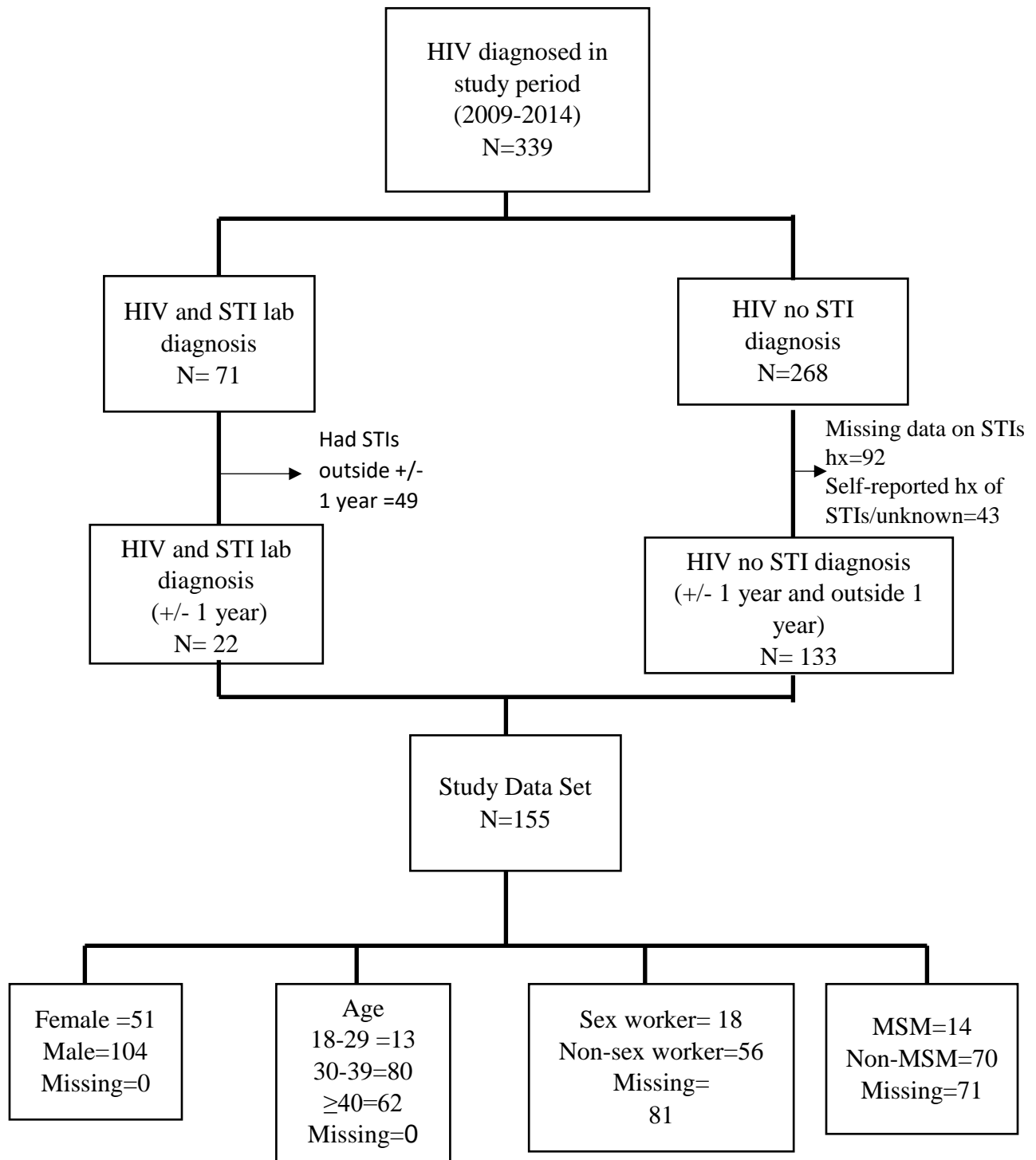
Initially data cleaning and management was conducted. During this process distribution of variables was done and variables of interest were determined with the aid of Statistical Package for the Social Sciences (SPSS) Statistics 20. Descriptive characteristics were summarized using frequencies and percentages. Association and level of significance between independent variables demographic (Gender, ethnicity, age), behavioral characteristics (IDU, MSM, heterosexual, sex work) and the risk for STI acquisition among PLWH were examined with bivariate logistic regression and Pearson chi-square. The level of significance to enter the multivariable model from the bivariate logistic regression was based on p-value  $< 0.20$ . Multivariable logistic regression at p-value  $< 0.05$ , was finally conducted, based on the Hosmer and Lemeshow purposeful forward selection criteria, on all significant variables in the bivariate analysis. This assessed their independent contribution to the risk for STIs acquisition in PLWH, after adjusting for other risk factors. Interaction between variables were also examined. Confounding was assessed for by using logistic regression. In addition, variables (counfounders) were also determined based on their clinical importance and the effect of their removal on the Beta coefficient ( $\geq 20\%$ ). Three models were constructed, the first and second model explored gender and IDU respectively, in addition to independent variables qualified for the multivariable model. The third model had the two risk factors of interest (IDU and gender) and other independent variables qualified for the multivariable model.



### **3.4 Results**

Three hundred and thirty nine (339) newly reported HIV clients were available for inclusion in our study , 71 of which had other STIs in PLWH. Of these, only 22 acquired other STIs in the year before and after HIV diagnosis, rendering the remaining 49 clients ineligible for comparison because they had STIs outside the window period of one year before and after HIV diagnosis.

The remaining 268 of the 339 HIV clients were eligible as cases without STIs, however 92 of these clients had missing data on history of STIs, leaving us with only 176. Of these 176 clients, 18 had history of previous STI, 23 answered “unknown” to history of previous STI and 2 answered “not asked” to history of previous STI. Thus, 43 clients were excluded from the cases without STIs, leaving us with 133 clients. Analysis was conducted on the 155 participants who were eligible for the study. Total occurrence of STIs among the study cases were 23 chlamydia, 9 cases of gonococcal infection, and 0 cases of syphilis within a year before and after HIV diagnosis. See figure 3.4 below for the summary of data set.



**Figure 3.4: Summary of data set**

### ***3.4.1 Study population characteristics***

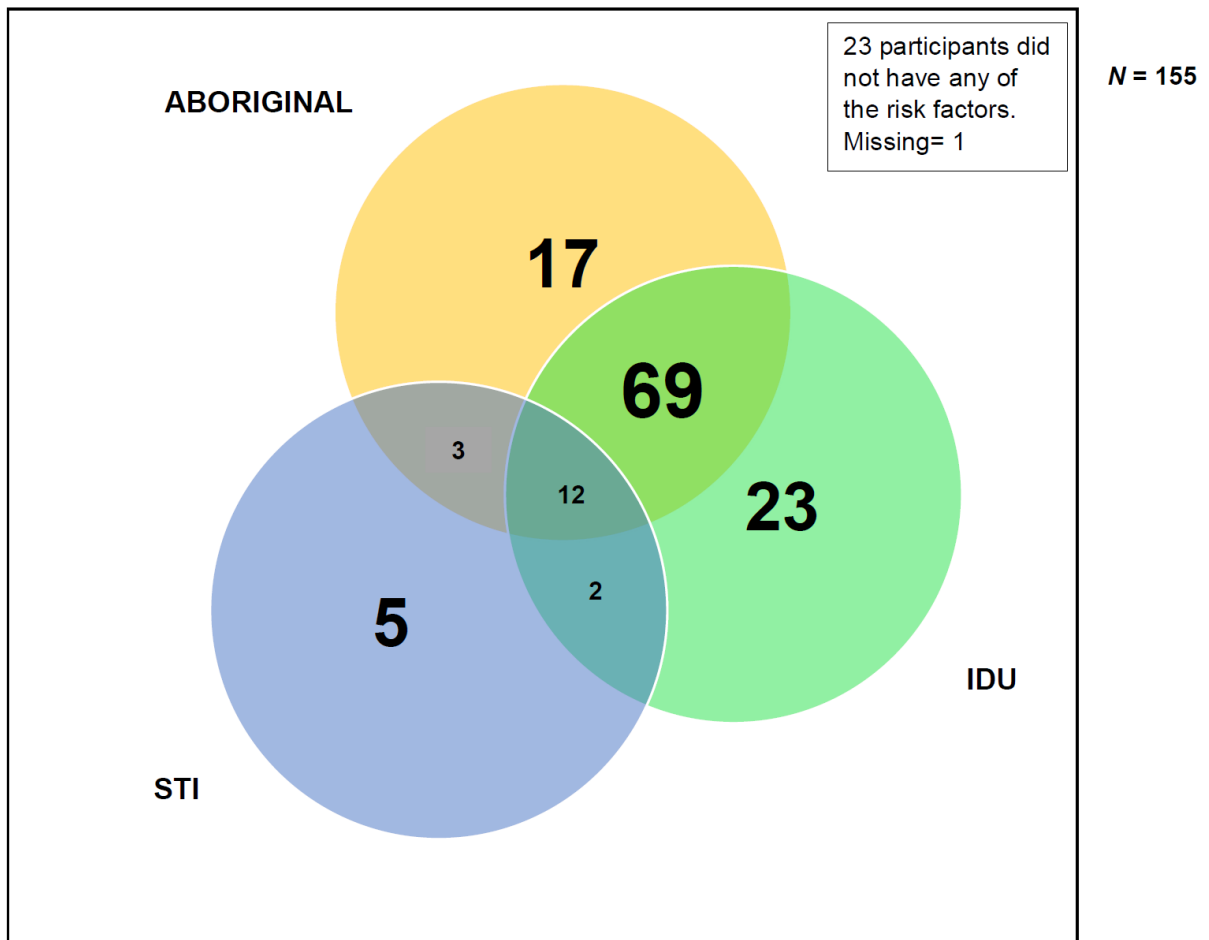
Table 3.4. Summarizes the demographic, behavioral and social characteristics of the study population. A total of 155 PLWH met the inclusion criteria for the study; 22 with STIs and 133 without. There is higher percentage of females and young individuals between ages 18 and 29 years among PLWH with STIs (within a year before and after HIV diagnosis) compared to PLWH without STIs.

In terms of behavioral characteristic, PLWH with STIs had a greater proportion of sex worker, and MSM compared to PLWH without STIs. Figure 3.5 illustrate that some of our participants have overlapping risk factors.

**Table 3.4: Baseline characteristics (N=155)**

<b>Variables</b>	<b>HIV and STI (YES=1) N (%)</b>	<b>HIV and STI (NO=0) N (%)</b>	<b>P-value</b>
<b>Gender</b>			
Female	14 (63.6%)	37 (27.8%)	<0.001
Male	8 (36.4%)	96 (72.2%)	
Missing/unknown	0	0	
<b>Injection drug use</b>			
Yes	14 (63.6%)	92 (73.2%)	0.37
No	8 (36.4%)	34 (26.8%)	
Missing/unknown	0	7	
<b>Age</b>			
18-29	6 (27.3%)	7 (5.3%)	<0.001
30-39	12 (54.5%)	68 (51.1%)	
≥40	4 (18.2%)	58 (43.6%)	
Missing/unknown	0	0	
<b>Ethnicity</b>			
Indigenous people	15 (71.4%)	86 (69.9%)	0.89
Non Indigenous people	6 (28.6%)	37 (30.1%)	
Missing/unknown	1	9	
<b>Sex Worker</b>			
Yes	6 (54.5%)	12 (19%)	0.01
No	5 (45.5%)	51 (81%)	
Missing/unknown	11	70	
<b>Men having sex with men</b>			
Yes	4 (33.3%)	10 (13.9%)	0.09
No	8 (66.7%)	62 (86.1%)	
Missing/unknown	10	61	
<b>Sex with confirmed HIV</b>			
Yes	8 (53.3%)	42 (40.0%)	0.33
No	7 (46.7%)	63 (60.0%)	
Missing/unknown	7	28	
<b>Heterosexualcontact no other risk</b>			
Yes	12 (92.3%)	65 (86.7%)	0.57
No	1 (7.7%)	10 (13.3%)	
Missing/unknown	9	58	
<b>Material deprivation quantiles</b>			
Not Deprived(Q1-Q3)	6 (27.3%)	32(29.1%)	0.86
Deprived(Q4-Q5)	16 (72.7%)	78(70.9%)	

Missing/unknown	0	23	
<b>Social deprivation quantiles</b>			
Not Deprived(Q1-Q3)	8 (36.4%)	31(28.2%)	0.44
Deprived(Q4-Q5)	14(63.6%)	79(71.8%)	
Missing/unknown	0	23	
<b>Total deprivation quantiles</b>			
Not Deprived(Q1-Q3)	7 (31.8%)	31(28.2%)	0.73
Deprived(Q4-Q5)	15 (68%)	79 (71.8%)	
Missing/unknown	0	23	



**Figure 3.5: Overlap between Indigenous people ethnicity, IDU, and STI (N=155)<sup>1</sup>**

<sup>1</sup> One participant had missing data for both IDU and Indigenous people

### ***3.4.2 Risk factors for acquisition of other STIs within a year before and after HIV diagnosis***

Table 3.5 shows a summary of bivariate analysis between each independent variable and STI acquisition in the year before and after HIV diagnosis. An association with the risk for STI acquisition was observed for: female gender, age, sex work, and MSM, even though their confidence intervals were wide. The wide confidence intervals could have resulted from the small sample size, and this could be narrowed if the sample size was increased. Other variables such as IDU, ethnicity, and deprivation quantiles were not associated with the risk for STI acquisition in the year before and after HIV diagnosis.

Gender, age, sex work, and MSM were chosen for inclusion in the multivariable model based on  $p\text{-value} < 0.20$ . Injection drug use was added to this model because it is one of the two risk factors of interest to be explored as contributing to the risk for STI acquisition in PLWH.

Table 3.6 and 3.7 show independent multivariable analysis with “gender” and “IDU” respectively. Table 3.8 shows multivariable analysis with all the variables qualified for the final model, however because of collinearity observed between gender and MSM, MSM was taken out of the final model. The multivariable analysis showed an association between female gender (OR 4.9), sex work (OR 5.0) and the risk for STI acquisition in the year before and after HIV diagnosis in SHR (See Table 3.8). Contrary to our expectation, IDU was not associated with the risk for STI acquisition in the year before and after HIV diagnosis (OR 0.20). No interaction was detected in the final multivariable models.

**Table 3.5: Bivariate analysis of factors associated with STI acquisition in the year before and after HIV diagnosis (N=155)**

<b>Variables</b>	<b>*OR (95%CI)</b>	<b>P-value</b>
<b>Gender</b>		
Male	1.0	
Female	4.5 (1.76 - 11.7)	<b>&lt;0.001</b>
<b>Intravenous Drug User</b>		
No	1.0	
Yes	0.7 (0.25-1.68)	0.37
<b>Age (years)</b>		
< 30	1.0	
30–39	0.2 (0.07–0.62)	<b>0.01</b>
≥ 40	0.1 (0.04–0.43)	<b>&lt;0.001</b>
<b>Ethnicity</b>		
Indigenous people	1.0	
Non- Indigenous people	0.9 (0.34-2.58)	0.89
<b>Sex Worker</b>		
No	1.0	
Yes	5.1 (1.33- 19.5)	<b>0.02</b>
<b>Heterosexual</b>		
No	1.0	
Yes	1.9 (0.22-15.8)	0.58
<b>Men having sex with men</b>		
No	1.0	
Yes	3.1 (0.79-12.2)	<b>0.11</b>
<b>Sex with confirmed/suspected HIV</b>		
No	1.0	
Yes	1.7 (0.58-5.08)	0.33
<b>Social deprivation quantiles</b>		
Not deprived (Q1-Q3)	1.0	
Deprived(Q4-Q5)	0.7 (0.26-1.8)	0.44
<b>Material deprivation quantiles</b>		
Not deprived(Q1-Q3)	1.0	
Deprived(Q4-Q5)	1.1 (0.39-3.05)	0.86
<b>Total deprivation quantiles</b>		
Not deprived (Q1-Q3)	1.0	
Deprived(Q4-Q5)	0.8(0.31-2.26)	0.73

\*OR- unadjusted odds ratio, CI Confidence interval



**Table 3.6: Multivariable analysis : factors associated with the risk for STI acquisition in the year before and after HIV diagnosis (Gender) (N=155)**

<b>Variables</b>	<b>*OR</b>	<b>P- value</b>
<b>Gender</b>		
Male	1.0	
Female	6.1(0.98. - 37.7)	0.05
<b>Men having sex with men</b>		
No	1.0	
Yes	10.4(1.18 -91.9)	0.04
<b>Sex Trade Work</b>		
No	1.0	
Yes	4.7(0.9 -23.7)	0.06
<b>Age</b>		
<30	1.0	
30-39	0.6(0.09 -3.7)	0.55
≥40	0.9(0.1 -6.6)	0.9

\*OR - Adjusted odds ratios, CI Confidence interval

**Table 3.7: Multivariable analysis : factors associated with the risk for STI acquisition in the year before and after HIV diagnosis (IDU) (N=155)**

<b>Variables</b>	<b>*OR</b>	<b>P- value</b>
<b>Injection drug use</b>		
No	1.0	
Yes	0.7(0.1 -3.9)	0.67
<b>M en having sex with men</b>		
No	1.0	
Yes	3.3(0.5 -23.2)	0.23
<b>Sex Work</b>		
No	1.0	
Yes	5.4(1.1 - 25.7)	0.03
<b>Age</b>		
<30	1.0	
30-39	0.6(0.1 -3.8)	0.6
≥40	0.6(0.1 -4.0)	0.6

\*OR - Adjusted odds ratios, CI Confidence interval

**Table 3.8: Multivariable analysis : factors associated with the risk for STI acquisition in the year before and after HIV diagnosis (Gender and IDU)(N=155)**

<b>Variables</b>	<b>*OR(95%CI)</b>	<b>P- value</b>
<b>Gender</b>		
Male	1.0	
Female	4.9(0.89 -27.3)	0.067
<b>Injection drug use</b>		
No	1.0	
Yes	0.2(0.03 -1.2)	0.08
<b>Sex Trade Work</b>		
No	1.0	
Yes	5.0(1.03 -24.6)	0.05
<b>Age</b>		
<30	1.0	
30-39	0.5(0.08 -2.7)	0.42
≥40	0.5(0.08 -2.5)	0.37

**\*OR - Adjusted odds ratios, CI Confidence interval**

### 3.5 Discussion

The analysis of SHR health service data showed that gender is associated with the risk for STI acquisition in the year before and after HIV diagnosis (OR 4.9), with marginal statistics significance. This shows that HIV-infected females have higher tendency for STIs acquisition within one year before and after HIV diagnosis in SHR compared to their male counterpart.

Our literature search did not find any study which examined risk factors for STI acquisition both before and after HIV diagnosis. There was also limited research that assessed risk factors that may affect STI acquisition before HIV diagnosis. However, a study by Kyriakos and colleagues indicated that a higher percentage of MSM and bisexual males had STI prior to HIV diagnosis, which was followed by IDU.(17) *Note that the studies reported below in this paper focussed on the risk for STI acquisition after HIV diagnosis.*

The association between female gender and the risk of having other STIs among PLWH has been reported by several other studies.(18-21) Romanoski *et al.* (2009), in their study conducted in Edmonton, Quebec, and Toronto, reported that females living with HIV have a higher risk of acquiring other STIs than HIV-infected males with OR 2.7. (21) This finding was supported by Belongia *et al.* in a study conducted in United State (US).(18) Belongia *et al.* (1997) examined new STIs cases in a population based cohort of PLWH between 1993 and 1994.(18) Data for this study were provided by the Minnesota department of health, and they noted that STIs acquisition was related to the female gender with OR 3.8.(18)

Conversely, other studies reported that males living with HIV were more likely to be infected with other STIs than females.(5, 22-24) In a medical record-based study by Erbeling *et al.* , 13.9% of 796 men and 11.9% of 354 women of PLWH were found to have acquired other STIs.(5) This observation was supported by Baffi *et al.* (22) Their analysis resulted in OR of 2.88 in favour of women, indicating that men living with HIV are at greater risk of acquiring STIs.(22) The discrepancy in these observations could have been due to the higher number of male participants in this study, as 76% of their participants were men. (22) It was also noted that majority of the men in this study were MSM, which is a high-risk group for STIs. (22) In addition, Baffi and colleagues examined only syphilis in PLWH, and most of the clients with this co-infection happened to be male(22). Manning *et al.*(2007) reported that about 80% of

PLWH who acquired STIs were male, and the majority of these men were also MSM. (24) On the other hand, Kalichman *et al.* (2011), in a systematic review, observed an identical prevalence of other STI in both HIV-infected women (15.8%) and men (13.6%), implying that both genders have almost the same likelihood of acquiring STIs.(25)

The association between female gender and STI acquisition might be due to a number of factors, one of which could be as a result of females reporting more STIs symptoms than males.(26) More women are generally observed to access medical care and services compared to men, and this could lead to more screening for STIs.(18) In addition, considering the efficient transmission of HIV from males to females (27), sexual violence against women could also contribute to their being infected with STIs.(28) Another potential reason for the acquisition of STIs among these women is the dependence on their husbands and sex partners for financial support. (29-32) This limits their say with regards to safe sex, and increases their odds of acquiring STIs. Biomedically, the wide vagina mucosa surface of women might also increase their tendency of STI acquisition. (21)

In our study, sex work was associated with the risk for STI acquisition in the year before and after HIV diagnosis with OR 5.0. The association between sex work and the acquisition of other STIs was supported by several other studies.(33-36) Hague and colleagues (2011) identified sex work to be significantly associated with STIs acquisition in PLWH with OR of 2.77.(35) This study noted that continuous engagement in high-risk sexual behavior, even after being diagnosed with HIV, was one of the reasons this subgroup was at risk of acquiring STIs.(35) This conclusion was seconded by Diaz *et al.*(34) Diaz *et al.*(2009), in a study conducted in Spain, observed that the OR of having syphilis and gonorrhea in sex workers living with HIV was 4.8 and 18.4 respectively, even though these measures of estimates were not significant.(34) Sex workers are then identified as an important population for the acquisition and transmission of other STIs and HIV.(37, 38)

Surprisingly, our analysis showed no association between IDU and the risk for STI acquisition in the year before and after HIV diagnosis in SHR (OR 0.2), having adjusted for potential confounders. Similar results have been observed in some other studies. (20, 23, 24) Manning *et al.* (2007) reported that IDU living with HIV are less likely to acquire STI when the STIs were analysed separately with OR 0.7, 0.8,0.5 for gonorrhea, syphilis, and chlamydia respectively.

(24) Baffi *et al.*(2010), in their study which explored illicit drug use as a variable and not IDU alone, did not notice an association between illicit drug use and acquisition of STI in persons with HIV with OR 1.14. (22)

This is not to say that the use of intravenous drugs is not associated with a tendency of high-risk sexual behavior. The use of these drugs alters mental capacity for making reasonable decisions regarding safe sex practises (10), thus increasing the possibility of STI acquisition in PLWH.(9) The presence of STIs in PLWH is a proxy marker that this group of individuals continuously engage in high-risk behavior,even after been diagnosed with HIV, causing transmission of other STIs and further HIV transmission and progression.(18)

Results from our analysis helped to pinpoint subgroups amongst PLWH that may be at high-risk of having STIs. These subgroups should be given high considerations in terms of program planning and interventions. Other subgroups should not be left out of intervention programs, because excluding these groups of PLWH will only result in an increase in STIs transmission amongst this population. The findings in our study might be different from that of other studies due to variation in study design, sample size and population characteristics.

Globally, HIV prevention programs do not consider routine screening for STIs in this population, which makes asymptomatic STIs undiagnosed and underreported.(24) In this case, health care providers should maximise every contact they have with PLWH by inquiring about high-risk behaviors such as high-risk sexual activity and substance abuse. (24) Individuals at risk of other STIs should also be screened during these contacts so that infections can be detected and treated on time because in most instances STIs may be asymptomatic, especially in women. (24, 35) The role of counselling should also be underscored in the reduction and prevention of STI acquisition in HIV. Some studies have observed a decrease in high-risk behaviors among individuals that tested for HIV after being counselled.(35) Therefore, PLWH should be engaged in regular counselling sessions during their visits to the health facilities. (24, 35) In our case, the message should center around the practise of safe sex (regular use of condoms) and safe use of intravenous drugs.

Prevention and reduction of STI acquisition amongst hard to reach population such as sex worker may be possible through community-based STI screening and treatment program. Several studies reported a high rate of STI screening and treatment with community based facilities.(40-42) A

study conducted by Poulin *et al.* among women with social problems, sex workers, and street youth, in Quebec City recorded that all their participants conceded to STI screening in their community based program.(40) Out of those with STI infection, 93% were treated.(40) Identical treatment rate had been documented earlier in other United State community based screening programs.(41, 42) Success in these programs may be due to several factors. This includes service delivery by “familiar and trusted community workers with a non-judgmental approach”, non-invasive mode of STI screening, and treatment by personal physician or community based clinic.(40;p.442, 43) Individuals not willing to use the conventional medical facilities had the choice of getting their treatment from community organization offices.(41) These services should not be available to sex workers alone, but their clients should also be partakers of such services in order to have lesser infections and complications.(44)

Two studies reviewed the effectiveness of HIV preventive programs for women at risk of HIV infection, one was conducted in Canada, United State, and Puerto Rico (45), and the other in United State.(46) They both reported that the most effective women HIV preventive programs had certain characteristics, which includes women only programs, gender based (power imbalance and sexual assertiveness), peer led, and requires several sessions.(45,46)These program characteristics also apply to HIV/STI preventive programs addressing sex worker.(44) STI preventive programs targeting women and sex worker should also consider addressing sexual violence in these population.(37, 43)

HIV/STI preventive programs should not only be individualistic-centered, but structural factors contributing to acquisition of these infections should also be given attention.(31,44) With the realization that an important factor that might contribute to STI acquisition in women is their financial dependence on their husbands and male partners(29-32), HIV/STI prevention strategies should include economic empowerment programs and policies.(31) More information on SES is available in Section 2.2.3. of this thesis. Programs addressing low SES in women may include microfinancing/micro credit program.(31, 47,48)This program provides loans to individuals with low income, who do not have steady employment, credit history, and collateral, thus helping with poverty alleviation, particularly in women.(31,47,48) Putting such program in place will empower these women, enabling them to have a say regarding safe sex practises, thus reducing their risk of STI acquisition.

Community empowerment programs underscoring self esteem and empowerment could also be targeted at women and sex workers.(46) These programs can help with skills development, enabling women to protect themselves from unsafe sex, and also strengthen their practice of safe sex.(44,46) Women enrolled in such program work together to tackle barriers to safer sex.(44)

Drug use has been observed to be common among sex workers (sex work harm), and also among women with male IDU sexual partners (30,49), thus harm reduction programs such as NEP could be incorporated into programs targeted at these subgroups.

Not one intervention programs can provide maximum HIV/STI prevention to these subgroups, however, combination of interventions at various levels (individual and structural) will provide ultimate reduction in the prevalence of these STIs.(44)

### **Strengths and limitations**

We acknowledge that health services data has limitations. Notwithstanding, it is better to have an insight to this problem using these data rather than not having any idea about the risk factors implicated in the acquisition of other STIs amongst PLWH in SHR.

As far as we know, this is the first study identifying risk factors for STIs acquisition among PLWH in SHR and Saskatchewan. It also adds to the body of knowledge regarding this association in Canada. Our study identified factors that could contribute to the acquisition of STIs within a year before and after HIV diagnosis in SHR. These factors would guide the choice of intervention programs. It further prevents the transmission of HIV, since SHR has the highest number of HIV cases in the province since 2005.(50,51)

The study had its own limitations. Gathering data on sensitive topics such as sexual orientation, engagement in sex work, and IDU could be challenging. Thus, the limited number of participants available for the analysis is a major limitation in this study. The marginal statistical association of gender, large confidence interval, non significant association for other covariates, and our inability to test interaction may be explained by inadequate statistical power due to our small sample size.

Also, we did not have the opportunity to compare differences in characteristic between participants whose data were included in the study and those not. Forty nine PLWH who acquired other STIs outside 365 days before and after HIV diagnosis were excluded from our



analysis. Also, ninety-two participants were excluded from the data set because of missing data on history of STIs. We acknowledge that the two groups may be significantly different and we have asked that caution be taken when interpreting the results of our study due to this limitation.

Even though our selection criteria identified a group without STIs, which was compared with those with STIs, we cannot overlook the fact that some participants in this group might not have been tested for STIs within 365 days of HIV diagnosis, resulting in their misclassification. Misclassification of this participants may distort the observed association between the independent variables (gender or IDU) and the risk for STI acquisition in the year before and after HIV diagnosis. Records of HIV and other reportable STIs do not follow individuals when they move from one health region to another, thus the accuracy of selecting a group without STIs may be compromised.

The primary sources of HIV exposure (risk factors) used for this analysis are not mutually exclusive, therefore there is a potential for misclassification. It remains to be determined if the association will be similar if the sources of HIV exposure were to be mutually exclusive.

The SHR data set had some data missing, these missing data could introduce some bias by affecting our effect estimate if the characteristics of the missing data differ from the characteristics of the used data

### 3.6 Conclusion

Recognition of risk factors contributing to acquisition of other STIs in PLWH is very crucial. Identifying these factors guides development of preventive programs that could reduce or prevent acquisition of other STIs among PLWH, and also prevent further HIV transmission. The knowledge of local epidemics with regard to HIV and other STIs transmission is very essential in the fight against HIV and STIs transmission.(47)

Findings from this study reveal that after adjusting for other independent variables, females are significant predictor of the risk for STI acquisition in the year before and after HIV diagnosis in SHR. Sex workers are also significant predictor of the risk for STI acquisition in the year before and after HIV diagnosis in SHR. However, IDU was not associated with this risk. Future studies with larger sample size, preferably a prospective cohort is needed to further explore these associations since there were no studies exploring the risk for STI acquisition before and after HIV diagnosis. This research will better inform evidence based public health practice targetted at reducing other STIs and HIV infection. The observed association between being a female and the risk of STI acquisition among PLWH shows it is important to understand factors that influence the acquisition of these STIs in women. A larger study looking specifically at women, and exploring factors that influence the acquisition of these STIs, is essential.

### 3.7 References

1. Galvin SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. *Nat Rev Microbiol*. 2004 Jan;2(1):33-42. PubMed PMID: 15035007.
2. Gomez GB, Ward H, Garnett GP. Risk Pathways for Gonorrhea Acquisition in Sex Workers: Can We Distinguish Confounding From an Exposure Effect Using A Priori Hypotheses? *The Journal of Infectious Diseases*. 2014;210(Suppl 2):S579-S85. PubMed PMID: PMC4231644.
3. Sheth P, Thorndycraft B. Fact sheet: sexually transmitted infections and HIV transmission. Toronto: Canadian Aids Treatment Information Exchange; 2009 [cited 2015 May 04]. Available from: <http://www.catie.ca/en/fact-sheets/epidemiology/sexually-transmitted-infections-and-hiv-transmission>.
4. Agmon-Levin N, Elbirt D, Asher I, Gradestein S, Werner B, Sthoeger Z. Syphilis and HIV co-infection in an Israeli HIV clinic: incidence and outcome. *Int J STD AIDS*. 2010 Apr;21(4):249-52. PubMed PMID: 20378895.
5. Erbedding EJ, Chung SE, Kamb ML, Irwin KL, Rompalo AM. New sexually transmitted diseases in HIV-infected patients: markers for ongoing HIV transmission behavior. *J Acquir Immune Defic Syndr*. 2003 Jun 01;33(2):247-52. PubMed PMID: 12794562.
6. Public Health Agency of Canada. Sexually Transmitted Infections—A Continued Public Health Concern Ottawa: Public Health Agency of Canada; 2013 [cited 2015 April 04 ]. Available from: <http://www.phac-aspc.gc.ca/cphorsphc-respcacsp/2013/sti-its-eng.php#figure-1>
7. Public Health Agency of Canada. Executive Summary - Report on Sexually Transmitted Infections in Canada: 2011 Ottawa: Public Health Agency of Canada; 2014 [cited 2015 February 10 ]. Available from: [www.phac-aspc.gc.ca/sti-its-surv-epi/index-eng.php](http://www.phac-aspc.gc.ca/sti-its-surv-epi/index-eng.php).
8. Saskatoon Health Region. Bloodborne and Sexually Transmitted Infections Saskatoon: Saskatoon Health Region; 2014 [cited 2015 February 10 ]. Available from: [https://www.saskatoonhealthregion.ca/locations\\_services/Services/Health-Observatory/Documents/Reports-Publications/2014\\_shr\\_series4\\_hsrfull.pdf](https://www.saskatoonhealthregion.ca/locations_services/Services/Health-Observatory/Documents/Reports-Publications/2014_shr_series4_hsrfull.pdf).

9. Des Jarlais DC, Arasteh K, McKnight C, Hagan H, Perlman DC, Semaan S. Associations Between Herpes Simplex Virus Type 2 and HCV With HIV Among Injecting Drug Users in New York City: The Current Importance of Sexual Transmission of HIV. *American Journal of Public Health*. 2011 01/17/accepted;101(7):1277-83. PubMed PMID: PMC3110210.
10. Bachmann LH, Grimley DM, Waithaka Y, Desmond R, Saag MS, Hook III EW. Sexually transmitted disease/HIV transmission risk behaviors and sexually transmitted disease prevalence among HIV-positive men receiving continuing care. *Sexually transmitted diseases*. 2005;32(1):20-6.
11. Saskatoon Health Region. Rates of HIV declining but more needs to be done Saskatoon: Saskatoon Health Region; 2014 [cited 2015 February 9]. Available from: [https://www.saskatoonhealthregion.ca/locations\\_services/Services/Health-Observatory/Documents/Reports-Publications/2014\\_shr\\_series5\\_hsrfull.pdf](https://www.saskatoonhealthregion.ca/locations_services/Services/Health-Observatory/Documents/Reports-Publications/2014_shr_series5_hsrfull.pdf).
12. Government of Saskatchewan. eHealth Saskatchewan Covered Population 2015 Regina: Government of Saskatchewan; 2015 [cited 2015 April 5]. Available from: <http://population.health.gov.sk.ca/>
13. Saskatoon Health Region. Saskatoon Health Region Demographics Saskatoon: Saskatoon Health Region; 2015 [cited 2015 February 9]. Available from: [http://www.communityview.ca/infographic\\_SHR\\_demographics\\_2014.html](http://www.communityview.ca/infographic_SHR_demographics_2014.html).
14. Saskatoon Health Region. First Nations and Métis Population Saskatoon: Saskatoon Health Region; 2014 [cited 2015 July 7]. Available from: [http://www.communityview.ca/pdfs/2014\\_SHR\\_FirstNations\\_Metis.pdf](http://www.communityview.ca/pdfs/2014_SHR_FirstNations_Metis.pdf).
15. Pampalon R, Hamel D, Gamache P. Health inequalities, deprivation, immigration and aboriginality in Canada: a geographic perspective. *Can J Public Health*. 2010 Nov-Dec;101(6):470-4. PubMed PMID: 21370783.
16. Public Health Observatory. Postal Code Database Saskatoon: Saskatoon Health Region; [cited 2015 2015 July].

17. Kyriakis KP, Hadjivassiliou M. HIV-1 Infection-Associated Risk Factors Among Sexually Transmitted Disease Patients in Athens, Greece: 1990 to 1996. *Sexually transmitted diseases*. 2000;27(5):259-65.
18. Belongia EA, Danila RN, Angamuthu V, Hickman CD, DeBOER JM, MacDONALD KL, et al. A Population-Based Study of Sexually Transmitted Disease Incidence and Risk Factors in Human Immunodeficiency Virus-Infected People. *Sexually transmitted diseases*. 1997;24(5):251-6.
19. Des Jarlais DC, McKnight C, Arasteh K, Feelemyer J, Perlman DC, Hagan H, et al. A perfect storm: crack cocaine, HSV-2, and HIV among non-injecting drug users in New York City. *Substance use & misuse*. 2014;49(7):783-92.
20. Do AN, Hanson DL, Dworkin MS, Jones JL. Risk factors for and trends in gonorrhea incidence among persons infected with HIV in the United States. *Aids*. 2001;15(9):1149-55.
21. Romanowski B, Myziuk LN, Walmsley SL, Trottier S, Singh AE, Houston S, et al. Seroprevalence and risk factors for herpes simplex virus infection in a population of HIV-infected patients in Canada. *Sexually transmitted diseases*. 2009;36(3):165-9.
22. Baffi CW, Aban I, Willig JH, Agrawal M, Mugavero MJ, Bachmann LH. New syphilis cases and concurrent STI screening in a southeastern US HIV clinic: a call to action. *AIDS patient care and STDs*. 2010;24(1):23-9.
23. Cicconi P, Cozzi-Lepri A, Orlando G, Matteelli A, Girardi E, Degli Esposti A, et al. Recent acquired STD and the use of HAART in the Italian Cohort of Naïve for Antiretrovirals (I. Co. NA): analysis of the incidence of newly acquired hepatitis B infection and syphilis. *Infection*. 2008;36(1):46-53.
24. Manning SE, Pfeiffer MR, Nash D, Blank S, Sackoff J, Schillinger J. Incident sexually transmitted infections among persons living with diagnosed HIV/AIDS in New York City, 2001–2002: a population-based assessment. *Sexually transmitted diseases*. 2007;34(12):1008-15.
25. Kalichman SC, Pelloso J, Turner C. Prevalence of sexually transmitted co-infections in people living with HIV/AIDS: systematic review with implications for using HIV treatments for prevention. *Sexually transmitted infections*. 2011;87(3):183-90.

26. Kalichman SC, Rompa D, Cage M. Sexually transmitted infections among HIV seropositive men and women. *Sexually transmitted infections*. 2000;76(5):350-4.
27. Des Jarlais DC, Boltaev A, Feelemyer J, Bramson H, Arasteh K, Phillips BW, et al. Gender disparities in HIV infection among persons who inject drugs in Central Asia: a systematic review and meta-analysis. *Drug and alcohol dependence*. 2013;132:S7-S12.
28. Des Jarlais DC, Feelemyer JP, Modi SN, Arasteh K, Hagan H. Are females who inject drugs at higher risk for HIV infection than males who inject drugs: an international systematic review of high seroprevalence areas. *Drug and alcohol dependence*. 2012;124(1):95-107.
29. Carovano K. More than mothers and whores: redefining the AIDS prevention needs of women. *International journal of health services*. 1991;21(1):131-42.
30. Clarke S, Keenan E, Bergin C, Lyons F, Hopkins S, Mulcahy F. The changing epidemiology of HIV infection in injecting drug users in Dublin, Ireland. *HIV medicine*. 2001;2(4):236-40.
31. Dean HD, Fenton KA. Addressing social determinants of health in the prevention and control of HIV/AIDS, viral hepatitis, sexually transmitted infections, and tuberculosis. SAGE Publications Sage CA: Los Angeles, CA; 2010.
32. Morison L. The global epidemiology of HIV/AIDS. *British Medical Bulletin*. 2001;58(1):7-18.
33. Bellis M, Cook P, Clark P, Syed Q, Hoskins A. Re-emerging syphilis in gay men: a case-control study of behavioural risk factors and HIV status. *Journal of Epidemiology and Community Health*. 2002;56(3):235-6.
34. Diaz A, Junquera M, Esteban V, Martínez B, Pueyo I, Suárez J, et al. HIV/STI co-infection among men who have sex with men in Spain. *Euro surveillance: bulletin European sur les maladies transmissibles= European communicable disease bulletin*. 2008;14(48):1424-7.
35. Hague JC, Muvva R, Miazad RM. STD coinfection and reinfection following HIV diagnosis: evidence of continued sexual risk behavior. *Sexually transmitted diseases*. 2011;38(4):347-8.

36. Williamson LM, Dodds JP, Mercey DE, Hart GJ, Johnson AM. Sexual risk behaviour and knowledge of HIV status among community samples of gay men in the UK. *Aids*. 2008;22(9):1063-70.
37. Cohan D, Kim A, Ruiz J, Morrow S, Reardon J, Lynch M, et al. Health indicators among low income women who report a history of sex work: the population based Northern California Young Women's Survey. *Sexually transmitted infections*. 2005;81(5):428-33.
38. Strathdee SA, Lozada R, Martinez G, Vera A, Rusch M, Nguyen L, et al. Social and structural factors associated with HIV infection among female sex workers who inject drugs in the Mexico-US border region. *PloS one*. 2011;6(4):e19048.
39. Shubber Z, Mishra S, Vesga JF, Boily M-C. The HIV Modes of Transmission model: a systematic review of its findings and adherence to guidelines. *Journal of the International AIDS Society*. 2014;17(1).
40. Poulin C, acuteeline, Alary M, Bernier F, Carbonneau D, Boily M-C, et al. Prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* among at-risk women, young sex workers, and street youth attending community organizations in Quebec City, Canada. *Sexually transmitted diseases*. 2001;28(8):437-43.
41. Gunn RA, Podschun GD, Fitzgerald S, Hovell MF, Farshy CE, Black CM, et al. Screening High-Risk Adolescent Males for *Chlamydia trachomatis* Infection: Obtaining Urine Specimens in the Field. *Sexually transmitted diseases*. 1998;25(1):49-52.
42. Jones CA, Knaup RC, Hayes M, Stoner BP. Urine screening for gonococcal and chlamydial infections at community-based organizations in a high-morbidity area. *Sexually transmitted diseases*. 2000;27(3):146-51.
43. Rekart ML. Sex-work harm reduction. *The Lancet*. 2006;366(9503):2123-34.
44. Steen R, Dallabetta G. Sexually transmitted infection control with sex workers: regular screening and presumptive treatment augment efforts to reduce risk and vulnerability. *Reproductive health matters*. 2003;11(22):74-90.
45. Exner TM, Seal DW, Ehrhardt AA. A review of HIV interventions for at-risk women. *AIDS and Behavior*. 1997;1(2):93-124.

46. Wingood GM, DiClemente RJ. HIV sexual risk reduction interventions for women: a review. *American journal of preventive medicine*. 1996.
47. Rahman A. Micro-credit initiatives for equitable and sustainable development: Who pays? *World development*. 1999;27(1):67-82.
48. Rankin KN. Governing development: neoliberalism, microcredit, and rational economic woman. *Economy and society*. 2001;30(1):18-37.
49. Volz E, Frost SD, Rothenberg R, Meyers LA. Epidemiological bridging by injection drug use drives an early HIV epidemic. *Epidemics*. 2010;2(3):155-64.
50. Neudorf C, Marko J, Wright J, Ugolini C, Kershaw T, Whitehead S, et al. Health Status Report 2008: A Report of the Chief Medical Health Officer Saskatoon: Saskatoon Health Region; 2008 [cited 2015 July 7]. Available from:  
[https://www.saskatoonhealthregion.ca/locations\\_services/Services/Health-Observatory/Documents/Reports-Publications/shr\\_health\\_status\\_report\\_2008\\_full.pdf](https://www.saskatoonhealthregion.ca/locations_services/Services/Health-Observatory/Documents/Reports-Publications/shr_health_status_report_2008_full.pdf).
51. Saskatchewan Ministry of Health. Saskatchewan's HIV Strategy 2010 – 2014. Regina: Saskatchewan Ministry of Health; [cited 2015 July 7]. Available from:  
<http://www.health.gov.sk.ca/hiv-strategy-2010-20>



## **Chapter 4: Manuscript 2: Is gender OR injection drug use a risk factor for acquiring sexually transmitted infections among people living with HIV in developed countries? A systematic review and meta-analysis.**

### **4.1 Abstract**

**Background:** The global impact of sexually transmitted infections (STIs) on health morbidity and mortality cannot be overemphasized, with about 40 million people PLWH and over 340 million newly diagnosed STIs (other than HIV) per year. The prevalence of STIs have been reported as high amongst PLWH.

**Objectives:** To determine if gender is a risk factor for acquiring other STIs in PLWH in developed countries. To determine if IDU is a risk factor for acquiring other STIs in PLWH in developed countries.

**Methods:** A systematic review and meta-analysis was conducted according to MOOSE and EPHPP recommendations. Its reporting was guided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Studies from developed countries addressing acquisition of other STIs in PLWH were identified for use in our study. Relevant data were abstracted and differences in OR across the studies and heterogeneity were examined using meta-analysis.

**Result:** Ten articles were reviewed for gender analysis, and these studies were conducted in four countries. The pooled OR for HIV-infected females acquiring other STIs compare to males was 1.38 (CI: 0.75 – 2.55; p-value= 0.30) with a high heterogeneity of  $I^2 = 96\%$ . For IDU analysis, six articles were reviewed from two countries. The pooled OR for IDUs acquiring other STIs compare to non-IDUs was 0.71 (CI: 0.4 -1.29; p-value=0.26) with a high heterogeneity of  $I^2 = 85\%$ .

**Conclusion:** The diagnoses of other STIs in PLWH suggest continuous exposure of non-infected individuals to both HIV and other STIs. Hence, public health practitioners globally should

prioritize intervention programs addressing behavioral activities that could lead to acquiring other STIs in PLWH.

## 4.2 Introduction

The global impact of sexually transmitted infections (STIs) on health morbidity and mortality cannot be overemphasized, with over 340 million newly diagnosed STIs (other than HIV) in 1999. (1) The prevalence of STIs have been reported high amongst PLWH. (2) Identifying other STIs in HIV-infected people suggest that these individuals continue to engage in high risk sexual behavior, exposing non-infected persons to HIV.(3, 4) The presence of these STIs expedite HIV progression and also its transmission.(3)

Considering the high prevalence of STIs in PLWH, it is important to identify the population at risk in order to reduce the risk of transmission of these STIs and also that of HIV.(5) This study earlier explored the independent relationship between gender and the risk *for* STI acquisition in the year before and after HIV diagnosis in Saskatoon Health Region. It also explored the relationship between IDU and the risk *for STI* acquisition in the year before and after HIV diagnosis, in SHR. However, because of the limitation of SHR health service data on the dependent variable (STIs in PLWH), and its limitation on potential risk factors, a systematic review and meta-analysis of studies exploring risk factors for the acquisition of other STIs in PLWH in developed countries was conducted. *Note that the risk for acquiring other STIs in HIV in this study considered STI acquisition after HIV diagnosis.*

The analysis explored developed countries because studies on risk factors for acquiring STIs in PLWH was also limited in Canada. We also took into consideration their comparable context to Canada. The review aims to determine if gender is a risk factor for acquiring STIs among PLWH in developed countries and to determine if IDU is a risk factor for acquiring STIs among PLWH in developed countries.

## 4.3 Methods

This systematic review and meta-analysis was conducted according to MOOSE (6), and EPHPP (7) recommendations. Its reporting was guided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, 2009 revision (8).

## **Research Protocol**

The research protocol provides a description of the methods that were applied to carry out the review. For this study, the protocol involves identifying inclusion and exclusion criteria, search terms, study quality descriptors, and data synthesis procedures.

### ***4.3.1 Criteria for considering studies for meta-analysis (Inclusion and exclusion criteria)***

#### ***Types of studies***

Observational studies were included in this review and analysis. These include cohort, case-control, longitudinal, and cross-sectional studies.

#### ***Country/Location for the study***

The review included studies conducted in developed countries. Developed countries classification for this study was based on the United Nations classification of countries.(9)

#### ***Types of participants and recruitment center***

Studies considered for this review had their population sample made up of individuals with HIV or drug users with HIV. Both male and female samples were included for the gender analysis. HIV- infected male and female who acquired other STIs were also included . Injection drug user and non-IDU were used for the IDU analysis.

Recruitment sites for the studies were grouped into three broad categories: illicit drug treatment center, infectious/HIV/STI clinic, and hospital outpatient clinics. Studies included in this review were from any of the three mentioned centers.

#### ***Measurement of study outcome***

The outcome of the review is the risk of acquiring other STIs amongst PLWH. For a study to be eligible for review and analysis, HIV and other STIs in the study were reported to have been previously diagnosed by the physician or laboratory diagnosed. This was to avoid information bias that can be created by self-reporting.

## ***Language***

Only articles written in English language were considered for the analysis.

## ***Study years included***

The search included publications from January 1985, when HIV antibody testing became generally available to December 2016. Thus, studies before 1985 even when relevant were excluded.

### ***4.3.2 Data sources and search strategy***

In order to identify eligible papers for this study a comprehensive literature search was conducted using scientific database such as Medline, PubMed, Embase, Proquest Public Health, Web of science and Global Health. The reference list of the 6 most recent articles, relevant, and review articles were also manually searched. A search strategy was developed on MEDLINE (see appendix D), and this was translated to the remaining databases. This search strategy was developed for four concepts: Human immunodeficiency virus, risk factor (gender OR IDU), sexually transmitted infections, and country. The data search was done in close collaboration with a librarian, and it took place between October 2015 and December 10<sup>th</sup> 2016. Search terms used for MEDLINE are detailed below

**Table 4.1: Search term**

<b>Concept #1</b>	<b>Concept #2 (Risk factors)</b>		<b>Concept #3</b>	<b>Concept #4</b>
Human immunodeficiency virus	Injection drug use	Gender	Sexually transmitted infections	Country
HIV / human immunodeficiency syndrome/ human immun*/ HIV infection/ HIV infect*/ HIV prevalence /AIDS/acquire	Injecting drug abuse/ intravenous drug abuse/injecting drug user/Injection drug use/IDU/substance	Female and male	Sexually transmitted diseases/STD/ sexually transmitted infections/STI/syphilis/ treponema pallidum/chancr	Developed countries/developed nation OR use of names of the different qualified countries

immunodeficiency syndrome /acquire immun*	e abuse injection/inject* drug abuse/substance abuse inject*/heroin /heroin dependence/drug addiction		chancroid / Haemophilus ducreyi / neisseria gonorrhoeae/ gonorrhea / chlamydia trachomatis/ chlamydia infections /herpes genitalis /herpes simplex /herpesvirus 2/ lymphogranuloma venereum / trichomonas vaginitis	
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### ***4.3.3 Data collection and analysis***

#### ***4.3.3.1 Study Selection***

One investigator (GA) scanned titles of all generated articles to identify relevant papers in line with the study topic. Articles not written in English language and duplicate papers from different data bases were excluded. The articles were read in full, to be sure it contains all the inclusion criteria for the study.

#### ***4.3.3.2 Quality assessment***

The quality of eligible studies were assessed using the EPHPP quality assessment tool for quantitative studies and its dictionary (see appendix E & F).(7) This tool has been assessed to be reliable, with adequate content and construct validity.(10) It was also awarded a strong methodological rating by the National Collaborating Centre for Methods and Tools.(11) Extraction of the data was by GA, and it was verified by MS.

Two raters reviewed the study quality using the global rating scale (GA,MS)<sup>2</sup>. Six components were considered in the global rating and these includes selection bias, study design, confounding, blinding, data collection method, and withdrawal/ dropouts rates.(7) The global rating scale indicates the study is “strong” when none of its component has a weak rating, “moderate” when only one component has a weak rating and “weak” when two or more of its component has a weak rating.(7) The two reviewers then discussed the discrepancies from the extracted data and came to a unanimous decision.

#### ***4.3.3.3 Data abstraction***

Details of number of obtained references, number of retrieved full text papers, and number of included and excluded articles were documented. This data was managed in Endnote. Relevant data were abstracted from eligible articles and entered into a standard Excel template. The data covered information such as study authors, publication year, males and females living with HIV, number of PLWH using intravenous drugs , those not using intravenous drugs and those with HIV and other STIs, study design, and statistical indicator (OR). Two investigators reviewed the abstracted data (GA,JL)<sup>3</sup>. Extraction of the data was by GA, and it was verified by JL. Discrepancies were resolved through discussion. Relevant data were entered into the Review Manager (RevMan) software.

#### ***4.3.3.4 Statistical analyses (Meta-analysis)***

The ORs for acquiring other STIs amongst HIV- infected females to males were calculated from abstracted females and males HIV/STI prevalence. The ORs for IDU and non-IDU were also calculated and meta-analysis was carried out on them. Forest plot was used to illustrate these ORs, with their 95% confidence intervals at p-value <0.05. While funnel plots was used to assess for publication bias. Egger’s test was also used to assess for publication bias because unlike the funnel plot it affords the study a better objective means of evaluating the reliability of the result. Random effects was used for weighting of the ORs and heterogeneity in effects was assessed by visualising the graphical plot and using the I<sup>2</sup> statistic. Review Manager 5.3 was used for the analysis, but stats direct was used to calculate Egger’s test.

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<sup>2</sup> GA- Grace Akinjobi, MS -Michael Schwandt

<sup>3</sup> GA- Grace Akinjobi, JL-June Lim

## 4.4 Results

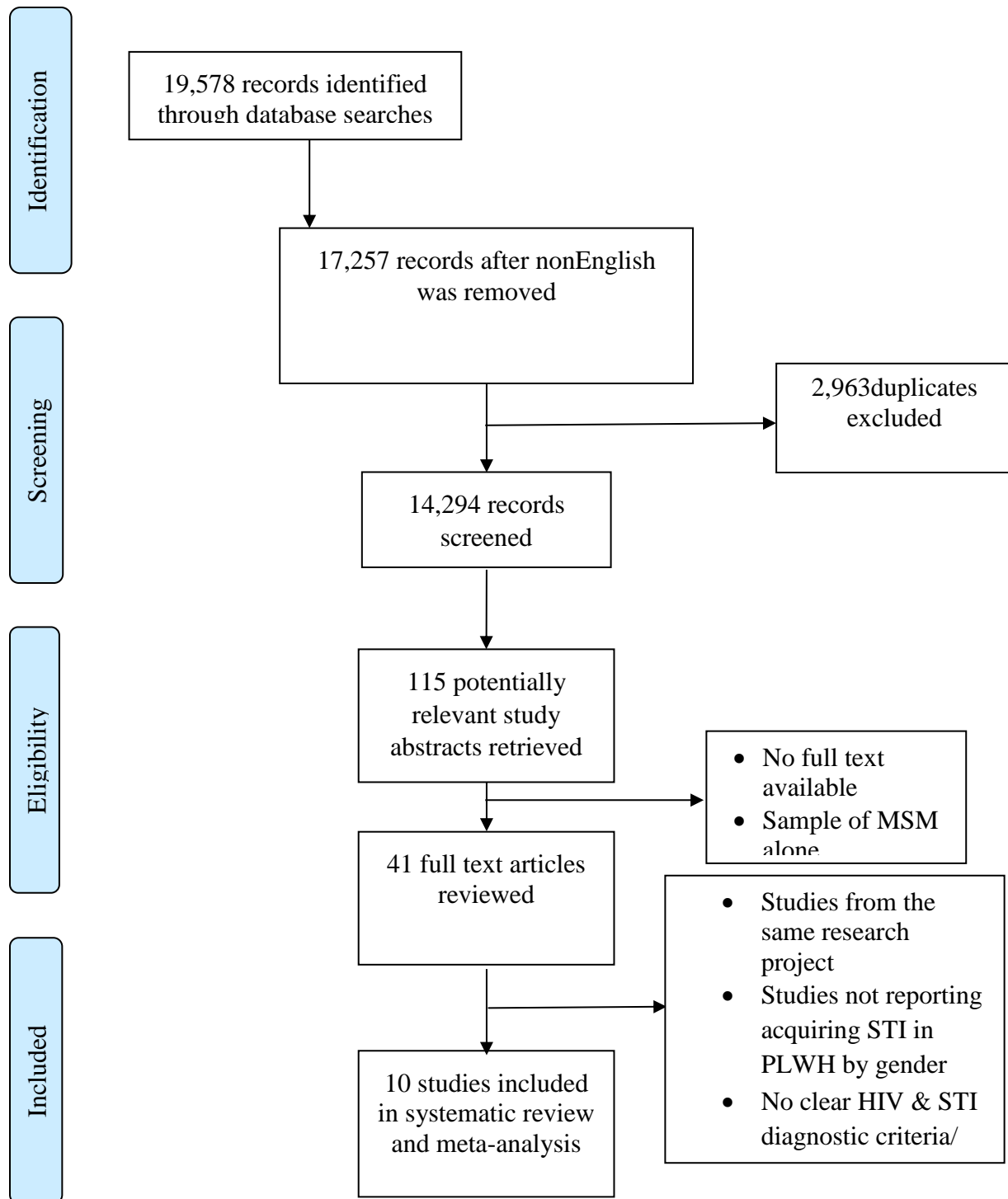
### Search results

Figure 4.1 and 4.2 shows the PRISMA outlines for the first (gender) and second (IDU) research questions, respectively. The two outlines illustrate the process of study selection.

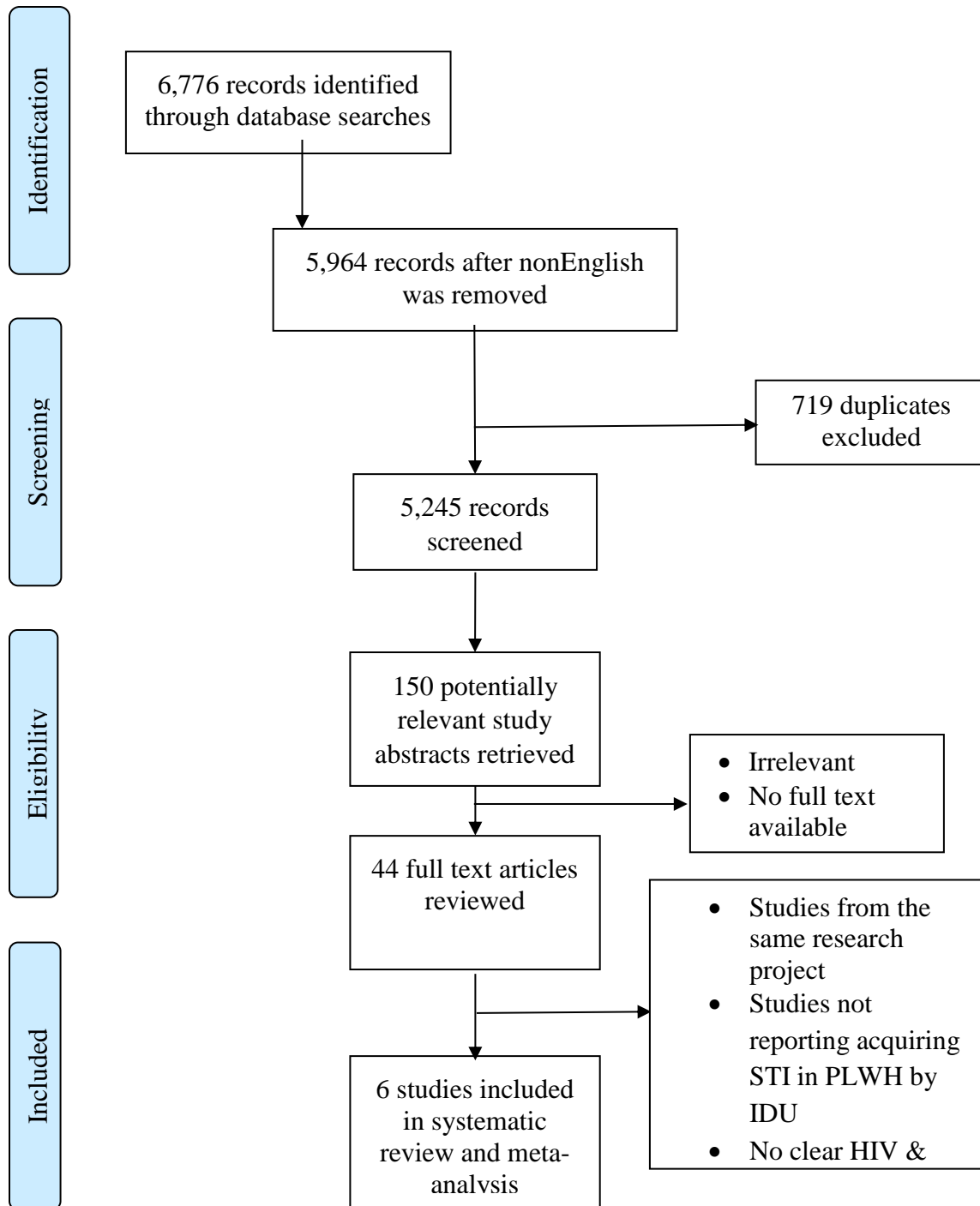
For “gender” search 19,578 titles were identified, out of which 2,321 non-English and 2,963 duplicates were excluded. One hundred and fifteen abstracts were retained after evaluation, and 41 of these articles were retrieved for detailed evaluation. Ten articles met the study inclusion criteria. Most articles were excluded because they were irrelevant, full text was not available, did not report acquisition of STIs in PLWH by gender, and did not have clear HIV and other STIs diagnostic criteria. Studies were also excluded due to incomplete data, lack of clarity on time of STI acquisition, studies from the same research project, and analysis based on the same population sample.

The “IDU” search produced 6,776 titles, out of which 812 were non-English and 719 duplicates were excluded. One hundred and fifty abstracts were retained after evaluation, and 44 of these articles were retrieved for detailed evaluation. Six articles met the study inclusion criteria. Articles were excluded from this analysis based on similar reasons above and not reporting acquisition of STIs in PLWH by IDU.





**Figure 4.1: PRISMA flow diagram: gender as a risk factor for acquiring other sexually transmitted infections in people living with HIV in developed countries**



**Figure 4.2: PRISMA flow diagram: injection drug use as a risk factor for acquiring other sexually transmitted infections in people living with HIV in developed countries**

### ***Is gender a risk factor for acquiring other STIs in PLWH in developed countries?***

#### **Study characteristics and quality**

Table 4.2 below summarizes study characteristics from the 10 included studies. Seven of the studies were conducted in the United States (3, 4, 12-16), and a study each from Canada, Italy, and Netherlands.(17-19) Three study designs were identified by the review. Out of the 10 studies, 4 were retrospective cohort studies (4, 12, 13, 15), 3 prospective cohort (3, 17, 18), and 3 cross sectional studies.(14, 16, 19) The settings for recruitment of participants for the studies vary per study. Majority of the studies, recruited study participants from HIV/STIs/infectious disease clinics.(3, 4, 12, 13, 16-19) The participants in 9 studies were PLWH (3, 4, 12, 13, 15-19), while that for the remaining one were illicit drug users with HIV.(14) Do (2001) followed up their cohort for 7 years (15), while Kalichman (2000) only followed theirs for 9 months.(3) Studies in this review captured STIs either by laboratory diagnosis or using a set definition.(3, 4, 12-19) In five studies STIs were measured using laboratory diagnosis only (12, 14, 15, 17, 18), four used sets of definition (3, 4, 16, 19), and only one captured STIs using laboratory diagnosis together with a definition.(13) Sexually transmitted infections studied in the included papers varied by studies, with 2 studies exploring HSV (14, 19), 2 on syphilis (12, 17), 1 on gonorrhea (15), and the remaining five had multiple STIs explored.(3, 4, 13, 16, 18)

Table 4.3 below summarizes quality of the included studies. The findings from the quality assessment showed that 6 out of 10 studies had a weak methodological rating (3, 13, 14, 16, 18, 19), 3 had a moderate rating (4, 12, 17), and the last a strong rating.(15) Since the inclusion and exclusion criteria for this review exclude quality assessment findings of the studies, all ten studies were included in the review.

**Table 4.2: Summary of characteristics of included studies (Gender)**

Study name	Country	Study design	Population	Type of STIs	STI def.	STI diag.	Exposure	Follow up	Recruitment site
Baffi (2010)	USA	RC	PLWH	Syp		RPR	MSM, HET, IDU	Not Available	HIV clinic
Belongia (1996)	USA	RC	PLWH	Syp, GC, CH	diagnosed STI	Culture, FTA	MSM, IDU, HET	Not Available	HIV clinic, hospitals
Cicconi (2008)	Italy	PC	PLWH	Syp		TPHA	MSM, IDU, HET	Not Available	Infectious disease clinics
Des Jarlais (2014)	USA	CS	Drug users with HIV	HSV		ELISA	MSM, IDU, HET	NA	Illicit drug treatment center
Do (2001)	USA	RC	PLWH	GC		culture or gram-stain	MSM, IDU, HET	7years	Hospitals, outpatient clinics, emergency room
Heiligenberg (2012)	Netherland	PC	PLWH	GC, CH, Syp		Nucleic acid amplification test, RPR	HET	Not Available	HIV clinic
Kalichman (2011)	USA	CS	PLWH	GC, CH, Tri, Syp, HSV	diagnosed STI		HET, IDU	NA	HIV clinic Infectious disease clinic Snowball

									technique
Kalichman (2000)	USA	PC	PLWH	GC,CH, NGU, Tri, Syp, HSV	diagnosis of an STI in the last 3months			9months	Infectious disease clinics
Manning (2007)	USA	RC	PLWH	GC,CH, Syp	STI diagnosed after HIV diagnosis		MSM, IDU,HET	Not Available	HIV clinic Infectious disease clinic Hospitals
Romanowski (2009)	Canada	CS	PLWH	HSV	history of herpes		MSM, HET, IDU, persons from endemic country, persons that have sex with someone	NA	Infectious disease clinic

## Legend

CS- Cross sectional

PC- Prospective cohort

L- Longitudinal

RC- Retrospective cohort

HSV-Herpes simplex virus

HET- Heterosexual

TPHA- Treponema pallidum Hemagglutination assay

GC- Gonorrhea

CH- Chlamydia

Syp- Syphilis

Tri- Trichomonas

HPV- Human papilloma virus

NA- Not applicable

NGU- Non gonococcal urethritis

FTA- Fluorescent treponemal antibody

RPR - Rapid plasma reagin

HOM- Homosexual

**Table 4.3: Summary of quality of the included studies (Gender)**

Study name	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawals and Drop-outs	Conclusion
Baffi (2010)	Moderate	Moderate	Moderate	Not Applicable	Moderate	Weak	Moderate
Belongia (1996)	Moderate	Moderate	Weak	Not Applicable	Moderate	Weak	Weak
Cicconi (2008)	Moderate	Moderate	Strong	Not Applicable	Moderate	Weak	Moderate
Des Jarlais (2014)	Moderate	Weak	Weak	Not Applicable	Moderate	Moderate	Weak
Do (2001)	Moderate	Moderate	Strong	Not Applicable	Moderate	Moderate	Strong
Heiligenberg (2012)	Moderate	Moderate	Weak	Not Applicable	Moderate	Weak	Weak
Kalichman (2011)	Weak	Weak	Moderate	Not Applicable	Weak	Moderate	Weak
Kalichman (2000)	Weak	Moderate	Weak	Not Applicable	Moderate	Moderate	Weak

Manning (2007)	Moderate	Moderate	Moderate	Not Applicable	Moderate	Weak	Moderate
Romanowski (2009)	Weak	Weak	Weak	Not Applicable	Moderate	Moderate	Weak



## **Data extraction**

Table 4.4 below summarizes data from the included studies. The 10 papers consist of 61,302 participants, 14, 559 females and 46,743 males.(3, 4, 12-19) Manning study had 1% of data for PLWH and 0.1% for HIV/STI missing, but it was still included in our analysis because we believe the available data could contribute to the explored association with only  $\leq 1\%$  missing data.

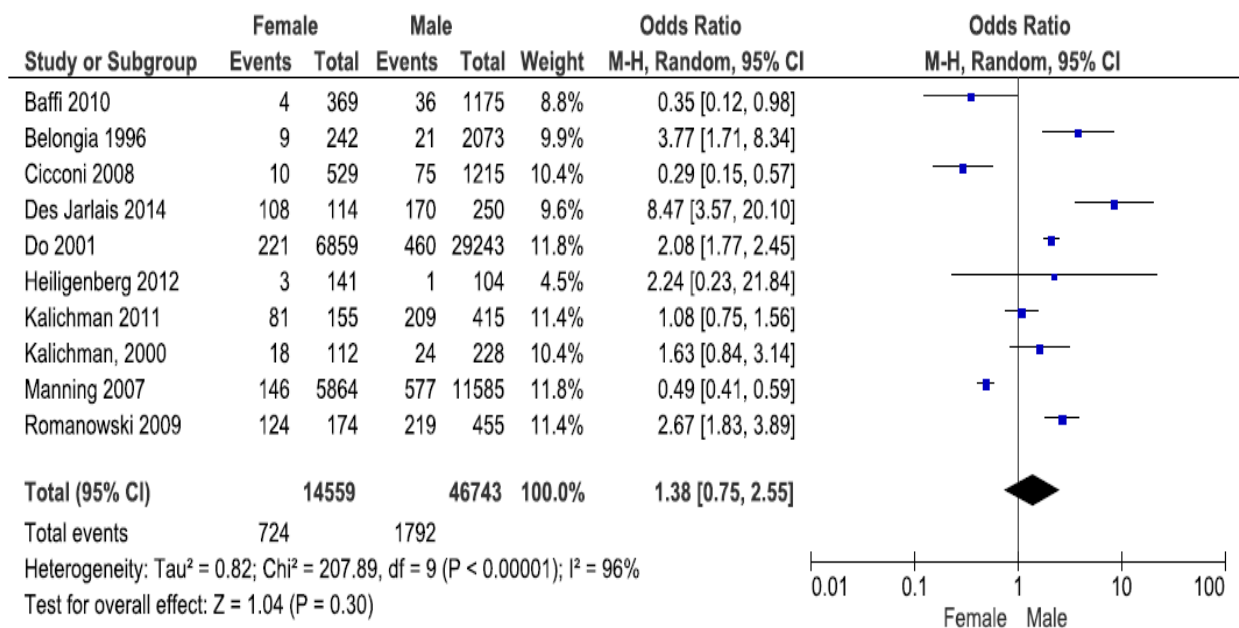
**Table 4.4: Summary of extracted data from included studies (Gender)**

Study name	Country	HIV/STI		HIV alone		OR (95%CI) <sup>1</sup>	p-value
		Females	Males	Females	Males		
Baffi (2010)	USA	4	36	369	1175	0.4(0.12-0.98)	0.05
Belongia (1996)	USA	9	21	242	2073	3.8(1.71-8.34)	<0.001
Cicconi (2008)	Italy	10	75	529	1215	0.3(0.15-0.57)	<0.001
Des Jarlais (2014)	USA	108	170	114	250	8.5 (3.57-20.1)	<0.001
Do (2001)	USA	221	460	6859	29243	2.1 (1.77-2.45)	<0.001
Heiligenberg (2012)	Netherland	3	1	141	104	2.2(0.23-21.8)	0.49
Kalichman (2011)	USA	81	209	155	415	1.08(0.75-1.56)	0.69
Kalichman (2000)	USA	18	24	112	228	1.63(0.84-3.14)	0.15
Manning (2007)	USA	146	577	5864	11585	0.5(0.41-0.59)	<0.001
Romanowski (2009)	Canada	124	219	174	455	2.7(1.83-3.89)	<0.001

<sup>1</sup> This is the odds of a female co-infected with HIV and other STIs compared to male

## Odds of HIV- infected female acquiring other STIs compared to male

These studies were ordered in forest plot and their effect estimates examined (see Figure 4.3). The OR for these studies (3, 4, 12-19), varies from 0.35 to 8.47, and 7 of these ORs (4, 12-15, 17, 19) were statistically significant .The pooled OR for females compared to males for acquiring STI's amongst PLWH was 1.38 with 95% CI ranging from 0.75 to 2.55 and p- value of 0.30 (see Figure 4.3).



**Figure 4.3: Forest plot of odds of HIV- infected female acquiring other sexually transmitted infections compared to male in developed countries**

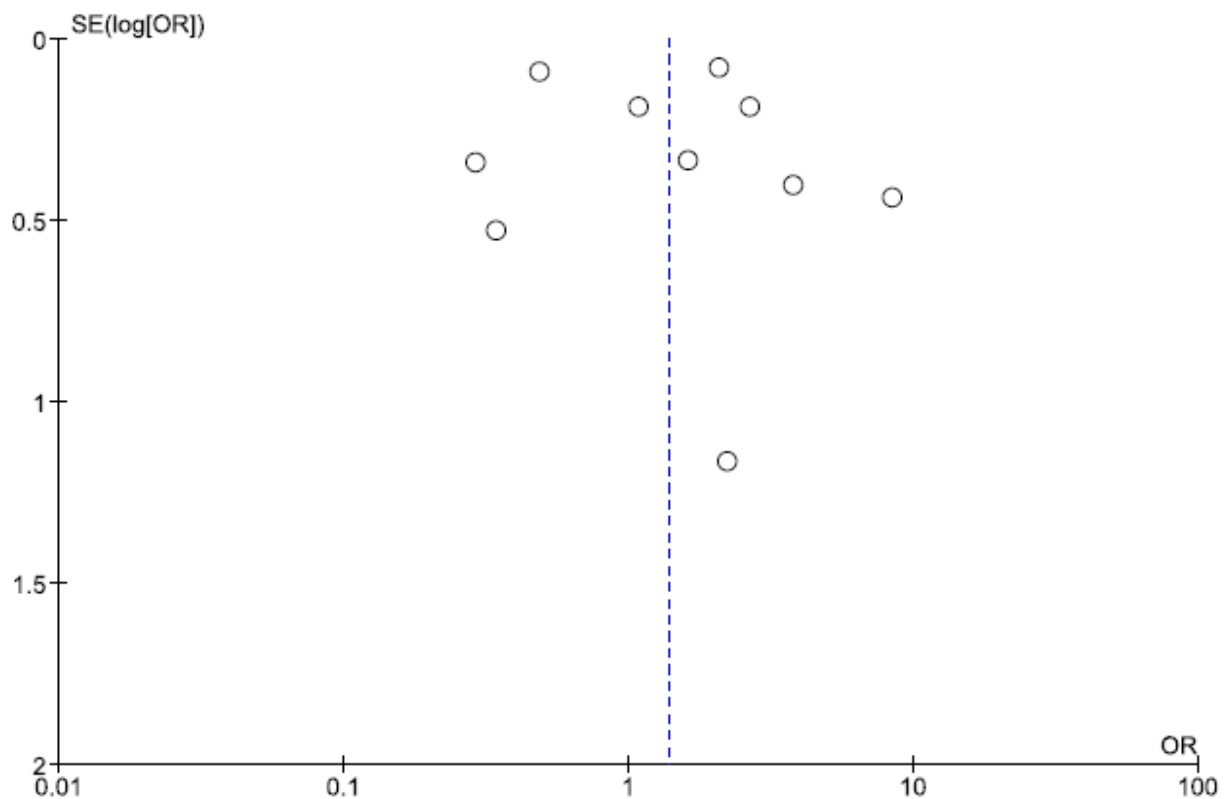
### Heterogeneity

Figure 4.3 shows forest plot illustrating the heterogeneity amongst ORs female: male for acquiring STI's amongst PLWH in developed countries . The effect estimates in this plot were on both sides of the reference line, with their confidence intervals poorly overlapping, suggesting

a high heterogeneity in the studies. This was supported by  $I^2$  at 96%,  $p$ -value  $<0.001$ . Note:  $I^2 > 40\%$  is regarded as high heterogeneity for this study.(20)

### Potential publication bias

Figure 4.4 depicts the funnel plot for the risk of acquiring STIs in a HIV- infected females compared to males in developed countries. The graph shows effect size (OR) on the x-axis and standard error of the log OR on the y-axis. The observed plot was asymmetrical and Egger's test  $p$ -value was 0.78.



**Figure 4.4: Funnel plot of odds of HIV- infected females acquiring other sexually transmitted infections compared to males in developed countries**

***Is Injection drug use a risk factor for acquiring other STIs in PLWH in developed countries?***

Table 4.5 below summarizes study characteristics from the 6 included studies. Five of these studies were conducted in the United States (4, 15, 16, 21, 22), while the remaining one was from Italy.(17) Three study designs were identified by the review. Out of the 6 studies, 3 were retrospective cohort studies (4, 15, 21), 2 prospective cohort(17, 22), and the remaining one a cross sectional study.(16) The settings for recruitment of participants for the studies vary per studies. Five studies recruited study participants from HIV/STIs clinics (4, 16, 17, 21, 22), and the last one from hospitals outpatient.(15) The participants in all 6 studies were PLWH (4, 15-17, 21, 22), and their follow up period ranges from 6 months to 7 years (15, 21, 22). Studies in this review captured STIs either from laboratory diagnosis or using a set definition (4, 15-17, 21, 22). In 2 studies (4, 16, ), STIs was measured using sets of definition only, 2 used laboratory diagnosis(15, 17) , and the last 2 captured STI using laboratory diagnosis together with a definition (21, 22). Sexually transmitted infections studied in the included papers varied by studies, with 4 studies exploring multiple STIs (4, 16, 21, 22), 1 on syphilis (17), and 1 on gonorrhoea.(15)

**Table 4.5: Summary of characteristics of included studies (IDU)**

Study name	Country	Study design	Population	Type of STIs	STI def.	STI diag.	Exposure	Definition of IDU	Follow up	Recruitment site
Cicconi (2008)	Italy	PC	PLWH	Syp		TPHA	MSM, IDU, HET		Not Available	Infectious disease clinics
Do (2001)	USA	RC	PLWH	GC		culture or gram-stain	MSM, IDU, HET	IDU in the 6mths prior/ at time of gonorrhea diagnosis and ART prescription	7yrs	Hospitals, outpatient clinics, emergency room
Hague (2011)	USA	RC	PLWH	GC, CH, Syp	STI in 30 days or more after	Nucleic Acid Amplification tests, RPR	MSM, IDU, HET, CSW	IDU during the 12 months before HIV or STI diagnosis	4yrs	STD clinic, private providers

					HIV diag- nosis					
Kalichman (2011)	USA	CS	PLWH	GC, CH, Tri, Syp, HSV	diag- nosed STI		HET, IDU		NA	HIV clinic Infectious disease clinic Snowball technique
Manning (2007)	USA	RC	PLWH	GC, CH, Syp	STI diag- nosed after HIV diagno- sis		MSM, IDU, HET		Not Avai- lable	HIV clinic Infectious disease clinic Hospitals
Mayer (2012)	USA	PC	PLWH	GC, CH, Syp	New STI diag- nosed at 6mths	Nucleic Acid Amplif-ication tests, VDRL,RPR, FTA	HET, IDU, HOM,	Injecting drugs at 6months	6mths	HIV clinic

## Legend

CS-	Cross sectional	GC- Gonorrhea	NGU-Non gonococcal urethritis
PC-	Prospective cohort	CH- Chlamydia	HSV-Herpes simplex virus
L-	Longitudinal	Tri-Trichomonas	FTA- Fluorescent treponemal antibody
RC-	Retrospective cohort	Syp- Syphilis	RPR- Rapid plasma reagin
HOM-	Homosexual	HPV- Human papilloma virus	
HET-	Heterosexual	NA-Not applicable	



**Table 4.6: Summary of quality of the included studies (IDU)**

Study name	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Conclusion
Cicconi (2008)	Moderate	Moderate	Strong	Not Applicable	Moderate	Weak	Moderate
Do (2001)	Moderate	Moderate	Strong	Not Applicable	Moderate	Moderate	Strong
Hague (2011)	Moderate	Moderate	Moderate	Not Applicable	Moderate	Moderate	Strong
Kalichman (2011)	Weak	Weak	Moderate	Not Applicable	Weak	Moderate	Weak
Manning (2007)	Moderate	Moderate	Moderate	Not Applicable	Moderate	Weak	Moderate
Mayer (2012)	Moderate	Moderate	Weak	Not Applicable	Moderate	Strong	Moderate

Table 4.6 above summarizes quality of the included studies. The methodological rating of the studies are as follows: 3 moderate (4, 17, 22), 2 strong (15, 21) , and the last was a weak rating.(16) Since the inclusion and exclusion criteria for this review do not include quality assessment findings of the studies, all 6 studies were included in the review.

### **Data extraction**

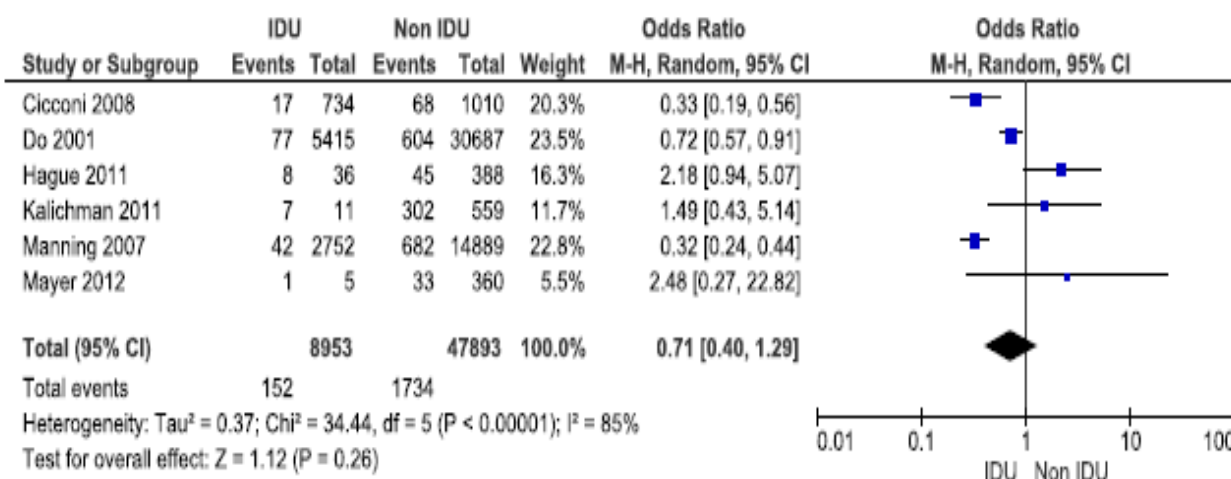
Table 4.7 below summarizes data from the included studies. The 6 papers included of 56,846 participants, 8,953 IDUs and 47,893 non-IDUs (4, 15-17, 21, 22).

These studies were ordered in forest plot and their effect estimates examined (see Figure 4.5 below). The OR's from the studies in this review ranged from 0.33 to 2.48, at p-value <0.05 (4, 15-17, 21, 22). The pooled OR for IDUs compared to non-IDUs for acquiring STI's amongst PLWH was 0.71 (95% CI: 0.4 -1.29; p-value-0.26) (see Figure 4.5 ).

**Table 4.7: Summary of extracted data from included studies (Injection Drug Use)**

Study name	Country	HIV/STI		HIV alone		OR (95%CI) <sup>2</sup>	P value
		IDU	NON IDU	IDU	NON IDU		
Cicconi (2008)	Italy	17	68	734	1010	0.33(0.19-0.56)	<0.001
Do (2001)	USA	77	604	5415	30687	0.7 (0.57-0.91)	0.01
Hague (2011)	USA	8	45	36	388	2.2 (0.94-5.07)	0.07
Kalichman (2011)	USA	7	302	11	559	1.5(0.43-5.14)	0.53
Manning (2007)	USA	42	682	2752	14889	0.32(0.24-0.44)	<0.001
Mayer (2012)	USA	1	33	5	360	2.5(0.27-22.8)	0.42

<sup>2</sup>This is the odds of an IDU PLWH co-infected with other STIs compared to non-IDU PLWH



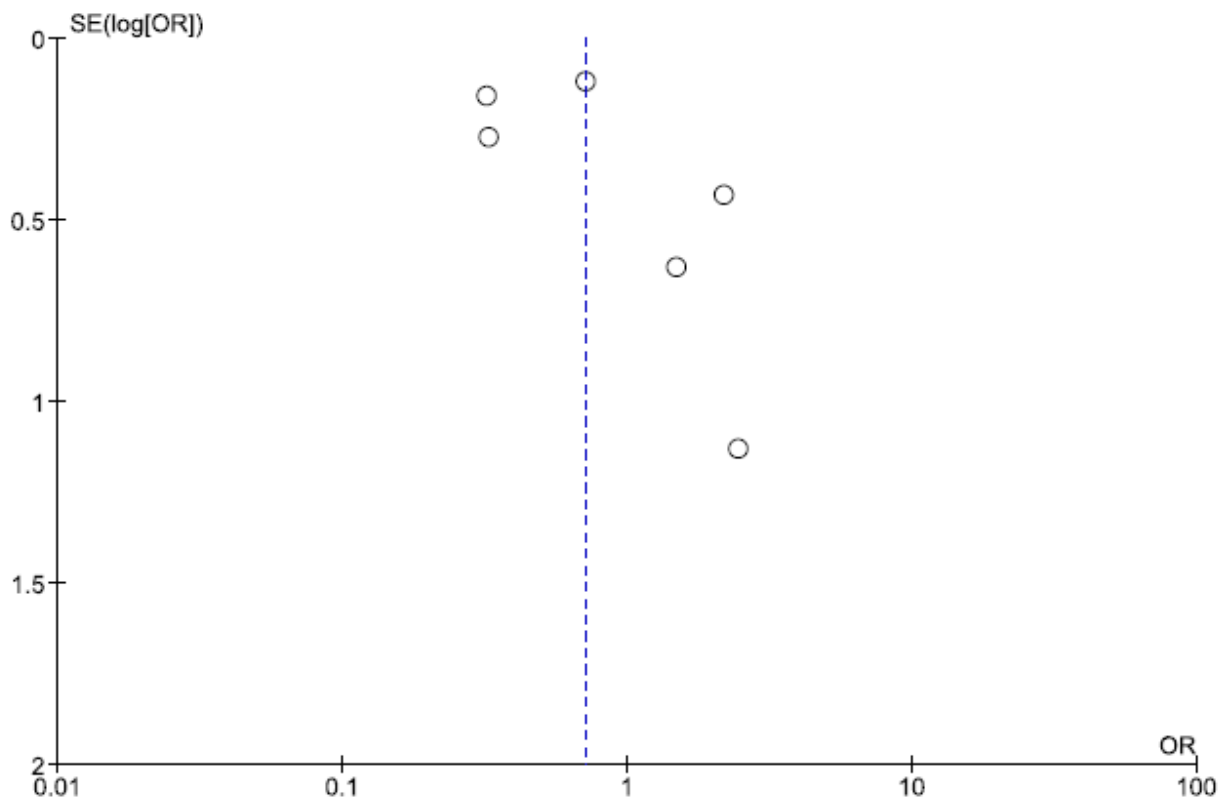
**Figure 4.5: Forest plot of injection drug use compared to non- injection drug use for acquiring sexually transmitted infections among people living with HIV in developed countries**

### Heterogeneity

Figure 4.5 above shows forest plot illustrating the heterogeneity amongst ORs for IDUs: non-IDUS for acquiring STIs amongst PLWH in developed countries. Here the effect estimates were observed on both sides of the reference line and their confidence intervals poorly overlap. This suggest a high level of heterogeneity. The high heterogeneity across the studies was again noted with  $I^2 = 85\%$  at  $p$ -value  $< 0.001$ .

### Potential publication bias

Figure 4.6 below illustrates a funnel plot for the risk of acquiring STIs in a HIV- infected IDUs compares to non-IDUs in developed countries. The observed plot was asymmetrical, while Egger's test p-value was 0.5.



**Figure 4.6: Funnel plot for the risk of acquiring sexually transmitted infections in HIV infected injection drug use compared to non- injection drug use in developed countries.**

## 4.5 Discussion

Globally, the prevalence of STIs has been reported to be high amongst PLWH (2) and this had led to increase in rate of the co-infection (4). Even though a comprehensive literature search of studies addressing the acquisition of other STIs amongst PLWH by gender and IDU was conducted, few studies were identified to fulfill our eligibility criteria. The limited articles were identified after screening 115 and 150 abstracts for the “gender” and “IDU” analysis respectively.

The first systematic review and meta-analysis (gender) identified and screened 19,578 published articles to review gender as a risk factor for acquisition of other STIs amongst PLWH in developed countries. Ten studies with 61,302 participants were eventually included in this review after the application of the inclusion and exclusion criteria. These studies were from 4 developed countries.

The pooled effect estimates for the studies were calculated by using the crude estimates from each publication. The sample size in each publication could affect the effect estimate made available for the metaanalysis. Studies with larger sample size are more likely to have higher power and precision compare to those with smaller sample size.

Findings for our gender query varies in the included studies. Some studies reported that HIV-infected females had a higher tendency to acquire other STIs compared to males.(13-15, 19)

These studies had documented various reasons that may be responsible for the acquisition of other STIs in women living with HIV. The study by Kalichman and colleagues in 2000 inferred that the OR might have been in favour of men because women report STI symptoms more than men.(3)

Belongia *et al.* (1996) reported that women were observed to use health care services more than men, therefore more women were screened for STIs compared to men (13). Heilligenberg *et al.*(2012), in a study conducted in Netherland, also screened more

HIV-infected women for STIs (58%) than men.(18) Romanoski *et al.* (2007), in a Canadian study exploring the acquisition of genital herpes in PLWH, also reported that HIV-infected females were more likely to be infected with other STIs than men.(19) These women were observed to have a higher tendency of STI acquisition because of their genital anatomy (wide vagina mucosa surface), which is prone to abrasions and lacerations during sexual intercourse. (19)

The acquisition of other STIs by HIV-infected females could also be accounted for by other factors, which has previously been reported to affect HIV transmission in women, one of which is their financial dependence on their husbands and partners. (23-26). This hinders their ability to have control over their body, and as such makes it difficult to negotiate safe sex (23-26), leading to increased risk of acquiring other STIs amongst HIV-infected women. One of the reviewed studies observed that more HIV-infected women than men with STI had a lower income even though the difference was minimal.(3) Some women with financial insecurity do engage in sex work in order to support themselves financially. (27) This act also limits their say in safe sex and increases their risk of having STIs. Another factor that could be responsible for the association between female gender and the likelihood of acquiring STIs in PLWH is sexual violence against women. (28) Females are reported to have a higher history of sexual violence compared to males.(28) Since male to female sexual transmission of HIV is more efficient than female to male transmission (29), these women are more likely to acquire other STIs than men.

Other studies documented that HIV-infected males are at higher risk of acquiring other STIs compare to females.(4, 12, 17) Baffi *et al.* (2011) reported that men living with HIV were more likely than women to be at risk of acquiring STIs.(12) The difference in their finding could have been as a result of more male participants in their study as 76% of their participants were male.(12) Sexual preference for majority of the men in this study was MSM, which is a group at high-risk of STIs.(12) Manning *et al.* (2007) confirmed Baffis result regarding this association.(4) The majority of participants in Manning's study were men involved in MSM practises (4).

Overall, the result from our meta-analysis showed no association between gender and the risk for acquiring other STIs amongst PLWH in developed countries. This observation was supported by Kalichman *et al.* (2011).(2) Kalichman and colleagues, in a systematic review, observed that HIV- infected females and males had similar risk for acquiring other STIs at 13.6% and 15.8% respectively(2).

The second systematic review and meta-analysis (IDU) identified and screened 6,776 published articles to review IDU as a risk factor for acquisition of other STIs amongst PLWH in developed countries. After the application of the inclusion and exclusion criteria, 6 studies with 56,846

participants were eventually included in this review. These studies were from two developed countries.

Findings from the IDU query showed that some studies suggested a possible risk of acquiring other STIs amongst IDUs living with HIV with OR 1.5 (0.43-5.14), 2.2 (0.94-5.07) , and 2.5 (0.27-22.8).(16, 21, 22) The observed odds by these studies might have been due to risky sexual behaviors amongst IDU.(16, 22) It was noted that PLWH continue having risky sexual behaviors after being diagnosed with HIV.(30, 31) Bachman *et al.* (2005), in a cross sectional study based on illicit drug use and not IDU alone, discovered that illicit drug users living with HIV are more likely to have STI compare to non users.(32) They observed that despite being infected with HIV, their participants still engage in unprotected sexual activities via various route (oral,vagina, receptive and insertive anal).(32) Bachman *et al.* also recorded a four times likelihood of engaging in high-risk sexual behavior when under the influence of illicit drugs.(32) Similarly, Stueve *et al.*, observed a relationship between high-risk sexual behavior and being “high” after the use of an illicit drug with OR of 1.66.(33)

In another study based on illicit drug use by Kalichman *et al.*(2000), HIV-infected persons on illicit drugs were almost two times more likely to acquire other STIs.(3) Kalichman and his colleagues also observed an increase in the rate of unprotected anal and vaginal sexual intercourse amongst these groups.(3) The results in these studies might have favoured non-drug users because the majority of their participants were males.(3, 32) This disproportional representation of males in these studies might be responsible for the results, particularly because men have a higher tendency of engaging in substance abuse.(34) Another factor that may be responsible for the illicit drug use association is the recruitment site. Study population for Kalichman research was from an infectious disease clinic (3), so it is likely that their sample was made up of HIV-infected substance users with STIs or symptoms of STIs infection.

Other studies did not report any association between acquiring other STIs amongst IDUs living with HIV (4, 15, 17), but none of these studies documented reasons for this finding.

Even though in other literature the prevalence of STIs tends to rise in the face of drug use (35, 36), this meta-analysis did not observe an association between IDU and the acquisition of other STIs amongst PLWH in developed countries.



The study heterogeneity for the gender and IDU analysis were both high at 96% and 85%, respectively. The high heterogeneity may have been due to dissimilarities in the studies with respect to participants, outcome, study design, risk of bias, and effect estimates. (20) The presence of enormous amount of heterogeneity amongst the studies reviewed for the two questions showed that the result of this study can not be generalized. Our findings points out that it is essential to know and understand one's local epidemic.(37)

The asymmetrical funnel plot observed in both analyses suggest the presence of publication bias. However, Egger's test p-value for the two analysis refute this observation. Thus, the asymmetrical funnel plot observed in our analysis could be due to other factors such as reporting bias, particularly since our study eliminated non- English studies. (20, 38) Another factor implicated for the asymmetrical funnel plot is the weak methodological rating of most of our studies, which leads to false overestimated effect estimates. (20, 38)

Even though there was no association between either gender or IDU and the risk of acquiring STIs among PLWH in developed countries, this does not imply that the two risk factors should be ignored in the fight against acquisition of STIs among PWLH. Rather, program development should take into consideration the essential needs of both males and females living with HIV. Also, special programs might be required to reach certain high-risk groups such as sex workers and IDUs. Some studies documented that IDUs living with HIV are less likely to use health services when compared to other PLWH.(39, 40)The use of intravenous drugs increases unsafe sexual behavior (14), and thus the possibility of transmitting or acquiring STIs in PLWH. While under the influence of drugs, decision-making is impaired and this gives the feeling of a rise in sexual pleasure that increases sexual activity.(14) This results in several risky sexual behaviors such as unprotected sex or having sex with multiple, casual, HIV-infected, or IDU partners.(32) Sexually transmitted infections can also be acquired in PLWH by exchanging sex for drugs or money to buy drugs.(14)

Reviewed studies emphasized that high-risk behaviors contribute a great deal to the likelihood of acquiring STIs in PLWH. Individuals living with HIV continuously engage in high risk sexual behavior, which increases their risk of acquiring other STIs and also transmission of HIV.(3, 4, 12, 32) Thus, high-risk sexual behavior and substance abuse should be given attention when considering intervention programs for this population (32).

Incorporating safe drug use program into sexual health programs is highly beneficial.(12) Relevant drug screening tools should be developed for use at the sexual health clinic.(12) Individuals established as having drug problems should then be referred to appropriate treatment facilities, such as supervised injection facilities (SIF). Supervised injection facilities could help decrease risky behavior, STIs, drug overdose, and death associated with illicit drug users.(41) During service delivery at these centers, emphasis should be placed on the risk of acquiring other STIs and also on further transmission of HIV. These programs will help to modify both sexual and drug use behaviors of at risk individuals with the final outcome of decreasing the prevalence of STI in PLWH.(3, 32)

Screening and treatment for STIs amongst PLWH, is another important useful intervention program.(3,15, 21, 32) Several studies have reported the difficulty in ascribing a temporal causation to the relationship between HIV and other STIs.(42) Even though, these STIs might have been discovered after HIV diagnosis, they might have been present in these individuals prior to HIV diagnosis (15, 43). Sexually transmitted infections remain undiagnosed without screening programs. Although, some nations have screening guidelines, health providers do not implement these guidelines.(12) Thus, STIs prevention policy in various countries should include educating the health providers to implement STIs guidelines aggressively. This move will help to reduce the incidence of STIs among PLWH.(12)

### **Strength and Limitations**

To the best of our knowledge, this is the first systematic review and meta-analyses examining if gender or IDU is a risk factor for acquiring other STIs amongst PLWH in developed countries. The presence of other STIs among PLWH is regarded as an indicator of high-risk sexual behaviors.(44) Exploring these factors helps to identify factors contributing to acquisition of other STIs in PLWH in developed countries, and subsequently guide the choice of intervention programs that can help to prevent other STIs.

With meta-analysis been the highest level of evidence in research, and the fact that a comprehensive, rigorous literature search, and screening according to MOSSE guideline was conducted, the findings from this study could help developed countries identify factors implicated in acquiring STIs in PLWH .

This systematic review and meta-analysis has some limitations that are worth noting. Limited number of articles were reviewed for the two research questions. This is an undeniable limitation. However, it is imperative that inclusion and exclusion criteria needs to be applied stringently.

Relevant data and information might have been missed by not using grey literature, although the grey literatures might have incomplete data.

Our systematic review and meta-analysis was limited by the quality of the original reviewed studies. However, since the data were gathered systematically from eligible studies it strengthens the associations of the risk factors (gender or IDU) and acquisition of other STIs in PLWH .

The weak methodological rating of most of the included articles is not a surprising finding in observational studies because all the mentioned components assessed in the EPHPP assessment tool are usually not well addressed in observational studies. However, the large number of participants in both reviews gave a high power and thus increases the impact of the study.

After applying the inclusion and exclusion criteria, the study ended up reviewing studies from 4 developed countries for the gender review, and only 2 developed countries for the IDU review, with the majority of the studies being from USA. This may affects its generalizability to other developed countries and even developing countries. However, because the sample size is large for both review we can attempt to adapt these findings.

Lastly, the high level of heterogeneity among the studies implies significant dissimilarities in the studies and their strength of association, however, the analysis still gave us insight into what the association between the risk factors (gender or IDU) and acquisition of other STIs in PLWH looks like. The heterogeneity in these analysis can be subsequently reduce by sub-group analysis. In- spite, of these limitations, the findings from the review is very essential for public and preventive health practitioners.

#### **4.6 Conclusion**

The presence of a large amount of heterogeneity amongst the studies reviewed for the two questions signals the importance of knowledge and understanding of local epidemics, such that intervention programs could be directed to the identified factors. In resource limited setting, programs should be prioritise for the HIV-infected subgroup, since they continue in their high-

risk behaviors after been diagnosed with HIV. These programs help to reduce the likelihood of acquiring other STIs, and subsequently decreases further HIV transmission.

In this meta-analysis, we explored the independent association of gender or IDU and acquisition of other STIs in PLWH in developed countries. The review observed no association between each of the risk factors and the risk of acquiring STIs in PLWH in developed countries. Due to the time frame of this study, we were not able to include non-English and grey studies in our analysis. Thus, another study exploring the same research question, but this time including non-English and grey studies in their review will be very useful. This will enrich study results by limiting publication and reporting bias. It will also increase the study power, and may help with generalization of study results. The propose study should also consider sub-group analysis in-order to reduce heterogeneity observed in our analysis.

## 4.7 References

1. Lewis DA, Latif AS, Ndowa F. WHO global strategy for the prevention and control of sexually transmitted infections: time for action. *Sex Transm Infect.* 2007 Dec;83(7):508-9. PubMed PMID: 18024710. Pubmed Central PMCID: 2598641.
2. Kalichman SC, Pellowski J, Turner C. Prevalence of sexually transmitted co-infections in people living with HIV/AIDS: systematic review with implications for using HIV treatments for prevention. *Sexually transmitted infections.* 2011;87(3):183-90.
3. Kalichman SC, Rompa D, Cage M. Sexually transmitted infections among HIV seropositive men and women. *Sexually transmitted infections.* 2000;76(5):350-4.
4. Manning SE, Pfeiffer MR, Nash D, Blank S, Sackoff J, Schillinger J. Incident sexually transmitted infections among persons living with diagnosed HIV/AIDS in New York City, 2001–2002: a population-based assessment. *Sexually transmitted diseases.* 2007;34(12):1008-15.
5. Erbedding EJ, Chung SE, Kamb ML, Irwin KL, Rompalo AM. New sexually transmitted diseases in HIV-infected patients: markers for ongoing HIV transmission behavior. *J Acquir Immune Defic Syndr.* 2003 Jun 01;33(2):247-52. PubMed PMID: 12794562.
6. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Jama.* 2000;283(15):2008-12.
7. Effective Public Health Practice Project. Quality assessment tool for quantitative studies Hamilton: Effective Public Health Practice Project; 2009 [cited 2016 March 20 ]. Available from: <http://www.ehphp.ca/tools.html>. .
8. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS med.* 2009;6(7):e1000097.
9. United Nation. World Economic Situation and Prospects: Country classification. New York: United Nation; 2014 [cited 2015 December 5 ]. Available from: [http://www.un.org/en/development/desa/policy/wesp/wesp\\_current/2014wesp\\_country\\_classification.pdf](http://www.un.org/en/development/desa/policy/wesp/wesp_current/2014wesp_country_classification.pdf).

10. Thomas B, Ciliska D, Dobbins M, Micucci S. A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. *Worldviews on Evidence-Based Nursing*. 2004;1(3):176-84.
11. National Collaborating Centre for Methods and Tools. Quality Assessment Tool for Quantitative Studies. 2016 [cited 2016 March 20 ]. Available from: [www.nccmt.ca/registry/view/eng/14.html](http://www.nccmt.ca/registry/view/eng/14.html).
12. Baffi CW, Aban I, Willig JH, Agrawal M, Mugavero MJ, Bachmann LH. New syphilis cases and concurrent STI screening in a southeastern US HIV clinic: a call to action. *AIDS patient care and STDs*. 2010;24(1):23-9.
13. Belongia EA, Danila RN, Angamuthu V, Hickman CD, DeBOER JM, MacDONALD KL, et al. A Population-Based Study of Sexually Transmitted Disease Incidence and Risk Factors in Human Immunodeficiency Virus-Infected People. *Sexually transmitted diseases*. 1997;24(5):251-6.
14. Des Jarlais DC, McKnight C, Arasteh K, Feelemyer J, Perlman DC, Hagan H, et al. A perfect storm: crack cocaine, HSV-2, and HIV among non-injecting drug users in New York City. *Substance use & misuse*. 2014;49(7):783-92.
15. Do AN, Hanson DL, Dworkin MS, Jones JL. Risk factors for and trends in gonorrhea incidence among persons infected with HIV in the United States. *Aids*. 2001;15(9):1149-55.
16. Kalichman SC, Cherry C, White D, Jones MI, Kalichman M. The Achilles' heel of HIV treatment for prevention: history of sexually transmitted coinfections among people living with HIV/AIDS receiving antiretroviral therapies. *Journal of the International Association of Physicians in AIDS Care*. 2011;10(6):365-72.
17. Cicconi P, Cozzi-Lepri A, Orlando G, Matteelli A, Girardi E, Degli Esposti A, et al. Recent acquired STD and the use of HAART in the Italian Cohort of Naive for Antiretrovirals (I. Co. NA): analysis of the incidence of newly acquired hepatitis B infection and syphilis. *Infection*. 2008;36(1):46-53.
18. Heiligenberg M, van der Loeff MFS, de Vries HJ, Speksnijder AG, Geerlings SE, Coutinho R, et al. Low prevalence of asymptomatic sexually transmitted infections in HIV-infected heterosexuals visiting an HIV clinic in the Netherlands. *AIDS*. 2012;26(5):646-9.

19. Romanowski B, Myziuk LN, Walmsley SL, Trottier S, Singh AE, Houston S, et al. Seroprevalence and risk factors for herpes simplex virus infection in a population of HIV-infected patients in Canada. *Sexually transmitted diseases*. 2009;36(3):165-9.
20. The Cochrane collaboration. *Cochrane Handbook for Systematic Reviews of Interventions* 2011 [cited 2016 April 10 ]. Available from: <http://handbook.cochrane.org/>.
21. Hague JC, Muvva R, Miazad RM. STD coinfection and reinfection following HIV diagnosis: evidence of continued sexual risk behavior. *Sexually transmitted diseases*. 2011;38(4):347-8.
22. Mayer KH, Bush T, Henry K, Overton T, Hammer J, Richardson J, et al. Ongoing sexually transmitted disease acquisition and risk taking behavior among US HIV-infected patients in primary care: Implications for prevention interventions. *Sexually transmitted diseases*. 2012;39(1):1.
23. Carovano K. More than mothers and whores: redefining the AIDS prevention needs of women. *International journal of health services*. 1991;21(1):131-42.
24. Clarke S, Keenan E, Bergin C, Lyons F, Hopkins S, Mulcahy F. The changing epidemiology of HIV infection in injecting drug users in Dublin, Ireland. *HIV medicine*. 2001;2(4):236-40.
25. Dean HD, Fenton KA. Addressing social determinants of health in the prevention and control of HIV/AIDS, viral hepatitis, sexually transmitted infections, and tuberculosis. SAGE Publications Sage CA: Los Angeles, CA; 2010.
26. Morison L. The global epidemiology of HIV/AIDS. *British Medical Bulletin*. 2001;58(1):7-18.
27. Van den Hoek J, van Haastrecht H, Scheeringa-Troost B, Goudsmit J, Coutinho R. HIV infection and STD in drug addicted prostitutes in Amsterdam: potential for heterosexual HIV transmission. *Genitourinary medicine*. 1989;65(3):146-50.
28. Des Jarlais DC, Feelemyer JP, Modi SN, Arasteh K, Hagan H. Are females who inject drugs at higher risk for HIV infection than males who inject drugs: an international systematic review of high seroprevalence areas. *Drug and alcohol dependence*. 2012;124(1):95-107.
29. Des Jarlais DC, Boltaev A, Feelemyer J, Bramson H, Arasteh K, Phillips BW, et al. Gender disparities in HIV infection among persons who inject drugs in Central Asia: a systematic review and meta-analysis. *Drug and alcohol dependence*. 2013;132:S7-S12.

30. Dublin S, Rosenberg PS, Goedert JJ. Patterns and predictors of high-risk sexual behavior in female partners of HIV-infected men with hemophilia. *Aids*. 1992;6(5):475-82.
31. Erbeling EJ, Stanton D, Quinn TC, Rompalo A. Behavioral and biologic evidence of persistent high-risk behavior in an HIV primary care population. *Aids*. 2000;14(3):297-301.
32. Bachmann LH, Grimley DM, Waithaka Y, Desmond R, Saag MS, Hook III EW. Sexually transmitted disease/HIV transmission risk behaviors and sexually transmitted disease prevalence among HIV-positive men receiving continuing care. *Sexually transmitted diseases*. 2005;32(1):20-6.
33. Stueve A, O'Donnell L, Duran R, San Doval A, Geier J. Being high and taking sexual risks: findings from a multisite survey of urban young men who have sex with men. *AIDS Education and Prevention*. 2002;14(6):482-95.
34. National institute of drug abuse. Sex and Gender Differences in Substance Use [cited 2017 January 17 ]. Available from: <https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use>.
35. Des Jarlais DC, Arasteh K, McKnight C, Hagan H, Perlman DC, Semaan S. Associations Between Herpes Simplex Virus Type 2 and HCV With HIV Among Injecting Drug Users in New York City: The Current Importance of Sexual Transmission of HIV. *American Journal of Public Health*. 2011 01/17/accepted;101(7):1277-83. PubMed PMID: PMC3110210.
36. Tyndall M, Patrick D, Spittal P, Li K, O'shaughnessy M, Schechter M. Risky sexual behaviours among injection drugs users with high HIV prevalence: implications for STD control. *Sexually Transmitted Infections*. 2002;78(suppl 1):i170-i5.
37. Kamb ML, Fishbein M, Douglas Jr JM, Rhodes F, Rogers J, Bolan G, et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. *Jama*. 1998;280(13):1161-7.
38. Sedgwick P. Meta-analyses: how to read a funnel plot. *BMJ*. 2013;346:f1342.
39. Jones JL, Hanson DL, Dworkin MS, Kaplan JE, Ward JW. Trends in AIDS-related opportunistic infections among men who have sex with men and among injecting drug users, 1991–1996. *Journal of Infectious Diseases*. 1998;178(1):114-20.



40. Solomon L, Stein M, Flynn C, Schuman P, Schoenbaum E, Moore J, et al. Health services use by urban women with or at risk for HIV-1 infection: the HIV Epidemiology Research Study (HERS). *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 1998;17(3):253-61.
41. Jozaghi E. Science versus politics: The need for supervised injection facilities in Montreal, Canada. *International Journal of Drug Policy*. 2012;23(5):420-1.
42. Katusiime C, Schlech WF, Parkes-Ratanshi R, Sempa J, Kambugu A. Characteristics of sexually transmitted infections among high-risk HIV-positive patients attending an urban clinic in Uganda. *Journal of the International Association of Providers of AIDS Care (JIAPAC)*. 2016;15(1):36-41.
43. Des Jarlais DC, Hagan H, Arasteh K, McKnight C, Perlman D, Friedman SR. Herpes simplex virus-2 and HIV among noninjecting drug users in New York City. *Sexually transmitted diseases*. 2007;34(11):923-7.
44. Hu Q-h, Xu J-j, Zou H-c, Liu J, Zhang J, Ding H-b, et al. Risk factors associated with prevalent and incident syphilis among an HIV-infected cohort in Northeast China. *BMC infectious diseases*. 2014;14(1):658.

## **Chapter 5: General discussion and conclusion**

This chapter will give a general discussion and conclusion on the study. The study explored the association between gender and the risk for STI acquisition in HIV in two manuscripts. It also explored IDU as a risk factor for STI acquisition in HIV. The first manuscript assessed the association between these variables using SHR health services data on PLWH, considering STIs acquired within a year before and after HIV diagnosis. The second manuscript explored these associations in developed countries through a systematic literature review and meta-analysis of studies. It considered STIs acquired after HIV diagnosis.

### **5.1. Manuscript 1**

The purpose of the first manuscript was to assess if either gender or IDU are risk factors for STI acquisition in the year before and after HIV diagnosis in SHR. This study was conducted due to the paucity of literature on acquisition of STIs among PLWH in SHR, and also in Canada. Saskatoon Health Region health services data on PLWH during the years 2009 to 2014 was used for the analysis. The study population was limited to reported HIV-infected patients with and without STI acquisition (within a year before and after HIV diagnosis). Our study compared two groups; the first had STI acquisition, while the second did not. Out of 339 newly reported HIV clients in SHR, 22 and 133 clients met the inclusion criteria for the first and second group respectively. The study was guided with the use of the proximate-determinants framework on distribution and determinants of HIV and other STIs (1), independent variables explored includes demographical and behavioral factors.

Our literature search did not reveal studies exploring risk factors for STI acquisition both before and after HIV diagnosis. Research which examined risk factors that may affect STI acquisition before HIV diagnosis were also very limited. Therefore, studies included in this paper explored the risk of STI acquisition after HIV diagnosis.

One of the findings from the first manuscript was that being a female significantly contributes to the risk for STI acquisition in the year before or after HIV diagnosis in SHR. Several studies exploring acquisition of STI post HIV diagnosis had similar findings .(2-5) While the results from some other studies contradicted ours.(6-8) There was no association between the use of intravenous drug and the risk for STI acquisition in the year before or after HIV diagnosis in the health region. This finding was backed by results from other studies which examined STI acquisition post HIV diagnosis.(4, 6, 8)

Sex work by PLWH in SHR was also found to be associated with the risk for STI acquisition in the year before and after HIV diagnosis. This observation was supported by a number of studies on STI acquisition post HIV diagnosis.(9-12)

Our study is the first of its kind in SHR and Saskatchewan that assessed factors contributing to the risk for STI acquisition in HIV. It also contributes immensely to the body of knowledge on this topic in Canada at large. The identification of risk factors (female, sex work) that may increase the risk for STI acquisition in HIV, could help guide public health practitioners and policy makers on what preventive program to focus on. Consequently, preventing or reducing acquisition and transmission of other STIs in PLWH, and also preventing further HIV transmission.

Even though, the study is the first of its kind to identify risk factors that could be responsible for STI acquisition among PLWH in SHR, its findings are prone to bias that could arise from selection of participants into the 2 groups compared for this study

## **5.2. Manuscript 2**

Systematic literature review and meta-analysis of studies exploring risk factors for acquiring STIs among PLWH in developed countries was conducted because of the limitation of SHR health services data. The systematic literature review and meta-analysis was amalgamated findings from published articles which explored factors that contribute to acquisition of other STIs in PLWH. Its first objective determined if gender is a risk factor for acquiring STIs among PLWH in developed countries. The second objective assessed if IDU is a risk factor for acquiring STIs among PLWH in developed countries. The review was conducted with groups of search terms: human immunodeficiency virus, risk factors (gender OR intravenous drug use), sexually transmitted infections, and develop countries. Scientific databases used for the search include: Medline, PubMed, Embase, Proquest, Public health, and Global health. Data screening,

extraction and quality assessment was then carried out by three reviewers. The review identified ten articles for the assessment of the association between gender and risk for acquiring STIs among PLWH in developed countries. In addition, it identified six studies to assess the association between IDU and risk for acquiring STIs among PLWH in developed countries.

The “gender” based systematic review, identified 6 of 10 reviewed articles to be of ‘weak’ quality (2, 3, 5, 13-15), 3 of moderate rating (6, 8, 16), and the last of strong methodological quality (4). Three study designs were identified by the review, this includes cross sectional studies (3, 5, 14), prospective (6, 13, 15), and retrospective cohort studies (2, 4, 8, 16). Four of the studies had the odds of HIV-infected female acquiring other STIs compared to that of males to be greater than 1 at p-value  $<0.05$ . (2-5) The forest plot ( Figure 4.3 ), illustrated a pooled OR for HIV-infected females acquiring other STIs compared to males as 1.38, CI (0.75-2.55), showing no association between gender and the risk for acquiring other STIs amongst PLWH in developed countries

The “IDU” based systematic review identified six studies to satisfy the inclusion criteria for the second query “To determine if IDU is a risk factor for acquiring STIs among PLWH in developed countries”. Half of these studies were found to have moderate methodological quality (6, 8, 17), 2 strong (4, 11), and the last had a weak rating (14). This review also identified three study designs, namely retrospective cohort (4, 8, 11), prospective cohort (6, 17), and cross sectional studies. (14) The OR for IDUs compared to non-IDUs for acquiring STIs among PLWH in this review ranged from 0.33 to 2.48 (4, 6, 8, 11, 14, 17), at p-value  $<0.05$ . The forest plot (Figure 4.5), showed a pooled OR for IDUs for acquiring STIs among PLWH compared to non-IDUs as 0.71, CI (0.40-1.29) indicating no association between IDU and the likelihood of having STIs among PLWH in developed countries.

Given the high heterogeneity observed amongst the studies, the review was not able to make a definitive conclusion on the independent association between gender or IDU and the risk of acquiring other STIs in PLWH in developed countries. The high heterogeneities could have resulted from variation in study design, population character, sample size, local condition and statistical analysis. In addition, a number of the studies used for the reviews were cross sectional studies, which have the limitation of ascertaining temporality of causation, even though some of the reviewed studies were cohort studies (retrospective and prospective).

### **5.3. Study Implications**

Human immunodeficiency virus disease progression has been and it is still a concern in this population, and an important factor to be considered in disease progression is the acquisition of other STIs. In that case, attention should be paid to factors identified by this study to be contributing to the acquisition of other STIs in PLWH in SHR, and the world at large. These may help reduce HIV transmission and progression.

The findings from this study will also inform public health practitioners and policy makers, such that they can make evidence based decisions. Public health practitioners and policy makers in resource limited setting could prioritize preventive programs, targeting reduction of STIs in PLWH based on our findings. The high heterogeneity in our review also implies that it is essential to be aware of one's local epidemic. A good understanding of local epidemics with respect to STI acquisition in HIV could help with effective program planning.

The result from the first manuscript showed that HIV-infected females were more at risk for STI acquisition in the year before and after HIV diagnosis. While that for the second manuscript showed no consistent and significant association between gender and the risk for acquiring STIs among PLWH in developed countries.

Even though, findings from the two manuscripts did not show an association between IDU and the risk for STI acquisition in HIV, existing literature does describe a relation between IDU and unsafe sexual behavior (15,18 Kalich 2000, Bachman 2005?), and subsequently the possibility of transmitting or acquiring STIs in PLWH. The use of drugs impairs the ability to make good decisions, which may lead to unsafe sexual practices.(3) Sexually transmitted infections can also be acquired in PLWH through exchange of sex for drugs or money to buy drugs.(3)

The above results do not imply that prevention and curative services should be restricted to females alone. Rather, both genders and their needs should be considered in program development because neglecting males could lead to a subsequent increase in the prevalence of STIs amongst PLWH. Special programs might also be necessary to reach certain high-risk groups.

It is important to note that behaviour does not necessarily change after HIV diagnosis, individuals with risk behaviour before HIV diagnosis often continue to engage in the same risks after being diagnosed with HIV infection.(11) Thus, intervention programs to address findings from both first and second manuscript may be similar.

The presence of STIs amongst PLWH is a major health issue. (19) These STIs further depress the immunity of an HIV-infected person (16), and also increase their VL. (20-22) This exposes them to frequent STIs acquisition, HIV transmission, and transmission of resistance strains for those on ART.(3, 15, 18, 23) Considering the effect of other STIs on PLWH both before and after HIV diagnosis, it is highly recommended to carry out regular STIs screening in high-risk individuals.(4, 11, 15, 16, 18) Particularly because STIs might be asymptomatic, especially in women.(4, 5, 24) Identifying and treating STIs promptly reduces the above mentioned risk.(5) In order to attain a reduction in the incidence of STIs both before and after HIV diagnosis, health care providers should also be dedicated to the use of STIs screening guidelines in various clinics.(16), particularly when in contact with a high risk client.

Another important aspect of intervention programs is to give consideration to is health promotion, health education, and behavioral counselling promoting messages on safe sex and drug use.(8, 25) It is important to note that all of the reviewed papers identified risky behavior amongst PLWH as a major factor facilitating acquisition of STI in PLWH. An important component of the health education messages should be consistent condom use.(4, 15, 18) Emphasis should also be placed on the risk for STI acquisition and further transmission of HIV during these sessions. In a US study among teenagers visiting STI clinic, 90% of males and 96.2% of females recorded inconsistent condom use with regular partners, and 64% of all participants with casual partners. (26) This finding was seconded by Minoz *et al.*, in their study in Spain, in which inconsistent condom use was recorded in 93.9% of their participants. (27) It is important to continuously remind PLWH about safe sex and drug practices to stop acquisition of

STIs among this group, and also prevent further HIV transmission.(3, 8, 25) It has been observed that emphasis during HIV counselling on avoiding risky behavior leads to behavioral changes. (28-32)

Even though, the two manuscripts did not explore the use of ART in PLWH, commencing ART in this population has been recommended to reduce the risk for STI acquisition in HIV.(3, 4) Availability of ART suppresses the viral load, and boost CD4 of these individuals, increasing their immunity (3, 4), thus reducing the risk of acquisition of other STIs in PLWH and further HIV transmission.(3, 4) The improvement in the CD4 and VL seen in this group might have been due to their continuous exposure to health education and behavioral counselling on safe sex and drug use practices, which usually occurs during their follow up sessions.(3, 4)

Depending on one's local epidemics, instituting appropriate reduction program might reduce acquisition of STIs in PLWH. Despite most countries involvement in NEP, HIV incidence from IDU still remain high (33), one of the reasons for the increase might be from habitual needle sharing.(34) This indicates that just making new needles available for this group is not enough to prevent high-risk behaviors. Countries could also consider supervised injection facilities (SIF) programs, in their fight to reduce high-risk behaviors.(35-37) A study conducted by Tyndall and colleagues (2006), recorded that out of over 4700 IDUs using the SIF, 2171 referrals were made.(37) These referrals were made to addiction counsellors, detoxification centers, community clinics, housing, and methadone centers.(37) This could eventually lead to the reduction in drug use, and subsequently a decrease in high risk sexual behavior.

The will power of policy makers is highly essential to the success of any preventive/public health program. The proposed SIFs in Montreal and Quebec were not only approved by the Supreme court, the program was also supported by the city.(35) The city came up with a multi - site approach, knowing that IDUs are distributed across the city.(35) However, the Montreal mayor refused SIF opening in one of the neighborhoods with large number of IDU.(35) In order to successfully prevent the acquisition of STIs in PLWH and also further HIV transmission, the will power of policy makers is greatly required. This is not just for SIF programs but for all programs, because they are the ones to make the resources (material and financial) available.

#### **5.4. Conclusion and future research directions**

After investigating SHR health services data on PLWH, the study found that being a female significantly contributes to the risk for STI acquisition in the year before and after HIV diagnosis, in SHR. On the contrary, use of intravenous drug was not found to be associated with STI acquisition in the year before and after HIV diagnosis in the region.

The systematic review and meta-analysis showed no association between gender or IDU and the risk of acquiring other STIs in PLWH in developed countries. High heterogeneity was detected amongst the studies, and this could have been due to variation in the studies included for the reviews. Considering the heterogeneity amongst the studies, the review might not be able to make a definitive conclusion on the independent association between gender or IDU and the risk of acquiring other STIs in PLWH in developed countries. The high heterogeneity in the second manuscript and the findings from the first suggest that it is essential to know one's local epidemics. This is key to prioritization of preventive programs.

Although findings from both manuscripts will contribute to bridging the knowledge gaps, with regards to independent relationship between gender or IDU and STI acquisition in HIV, more research is still needed to better understand these associations. Future research exploring these associations, and also considering STI acquisition after HIV diagnosis is highly necessary in both SHR and the world at large. This research should consider a larger sample size, and a longer follow up time. A larger sample size will increase the study power, while a longer follow up period will give time to identify factors that could contribute to the risk for STI acquisition in HIV. This will improve the quality of data available for analysis in this population. Another study with a larger participants, examining HIV-infected women only, and assessing factors that may influence their acquisition of other STIs will also be helpful.

The two suggested research will help to better understand these associations. These will better assist public health practitioners to make informed decision in terms of policy development and programs addressing acquisition of STIs in HIV.



## 5.5. References

1. Boerma JT, Weir SS. Integrating demographic and epidemiological approaches to research on HIV/AIDS: the proximate-determinants framework. *Journal of Infectious Diseases*. 2005;191(Supplement 1):S61-S7.
2. Belongia EA, Danila RN, Angamuthu V, Hickman CD, DeBOER JM, MacDONALD KL, et al. A Population-Based Study of Sexually Transmitted Disease Incidence and Risk Factors in Human Immunodeficiency Virus-Infected People. *Sexually transmitted diseases*. 1997;24(5):251-6.
3. Des Jarlais DC, McKnight C, Arasteh K, Feelemyer J, Perlman DC, Hagan H, et al. A perfect storm: crack cocaine, HSV-2, and HIV among non-injecting drug users in New York City. *Substance use & misuse*. 2014;49(7):783-92.
4. Do AN, Hanson DL, Dworkin MS, Jones JL. Risk factors for and trends in gonorrhea incidence among persons infected with HIV in the United States. *Aids*. 2001;15(9):1149-55.
5. Romanowski B, Myziuk LN, Walmsley SL, Trottier S, Singh AE, Houston S, et al. Seroprevalence and risk factors for herpes simplex virus infection in a population of HIV-infected patients in Canada. *Sexually transmitted diseases*. 2009;36(3):165-9.
6. Cicconi P, Cozzi-Lepri A, Orlando G, Matteelli A, Girardi E, Degli Esposti A, et al. Recent acquired STD and the use of HAART in the Italian Cohort of Naïve for Antiretrovirals (I. Co. NA): analysis of the incidence of newly acquired hepatitis B infection and syphilis. *Infection*. 2008;36(1):46-53.
7. Erbedding EJ, Chung SE, Kamb ML, Irwin KL, Rompalo AM. New sexually transmitted diseases in HIV-infected patients: markers for ongoing HIV transmission behavior. *J Acquir Immune Defic Syndr*. 2003 Jun 01;33(2):247-52. PubMed PMID: 12794562.
8. Manning SE, Pfeiffer MR, Nash D, Blank S, Sackoff J, Schillinger J. Incident sexually transmitted infections among persons living with diagnosed HIV/AIDS in New York City, 2001–2002: a population-based assessment. *Sexually transmitted diseases*. 2007;34(12):1008-15.
9. Bellis M, Cook P, Clark P, Syed Q, Hoskins A. Re-emerging syphilis in gay men: a case-control study of behavioural risk factors and HIV status. *Journal of Epidemiology and Community Health*. 2002;56(3):235-6.

10. Diaz A, Junquera M, Esteban V, Martínez B, Pueyo I, Suárez J, et al. HIV/STI co-infection among men who have sex with men in Spain. *Euro surveillance: bulletin Europeen sur les maladies transmissibles= European communicable disease bulletin*. 2008;14(48):1424-7.
11. Hague JC, Muvva R, Miazad RM. STD coinfection and reinfection following HIV diagnosis: evidence of continued sexual risk behavior. *Sexually transmitted diseases*. 2011;38(4):347-8.
12. Williamson LM, Dodds JP, Mercey DE, Hart GJ, Johnson AM. Sexual risk behaviour and knowledge of HIV status among community samples of gay men in the UK. *Aids*. 2008;22(9):1063-70.
13. Heiligenberg M, van der Loeff MFS, de Vries HJ, Speksnijder AG, Geerlings SE, Coutinho R, et al. Low prevalence of asymptomatic sexually transmitted infections in HIV-infected heterosexuals visiting an HIV clinic in the Netherlands. *AIDS*. 2012;26(5):646-9.
14. Kalichman SC, Cherry C, White D, Jones MI, Kalichman M. The Achilles' heel of HIV treatment for prevention: history of sexually transmitted coinfections among people living with HIV/AIDS receiving antiretroviral therapies. *Journal of the International Association of Physicians in AIDS Care*. 2011;10(6):365-72.
15. Kalichman SC, Rompa D, Cage M. Sexually transmitted infections among HIV seropositive men and women. *Sexually transmitted infections*. 2000;76(5):350-4.
16. Baffi CW, Aban I, Willig JH, Agrawal M, Mugavero MJ, Bachmann LH. New syphilis cases and concurrent STI screening in a southeastern US HIV clinic: a call to action. *AIDS patient care and STDs*. 2010;24(1):23-9.
17. Mayer KH, Bush T, Henry K, Overton T, Hammer J, Richardson J, et al. Ongoing sexually transmitted disease acquisition and risk taking behavior among US HIV-infected patients in primary care: implications for prevention interventions. *Sexually transmitted diseases*. 2012;39(1):1.
18. Bachmann LH, Grimley DM, Waithaka Y, Desmond R, Saag MS, Hook III EW. Sexually transmitted disease/HIV transmission risk behaviors and sexually transmitted disease prevalence among HIV-positive men receiving continuing care. *Sexually transmitted diseases*. 2005;32(1):20-6.

19. Kalichman SC, Pellowski J, Turner C. Prevalence of sexually transmitted co-infections in people living with HIV/AIDS: systematic review with implications for using HIV treatments for prevention. *Sexually transmitted infections*. 2011;87(3):183-90.
20. Chakraborty H, Sen PK, Helms RW, Vernazza PL, Fiscus SA, Eron JJ, et al. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. *Aids*. 2001;15(5):621-7.
21. Hughes G, Field N. The epidemiology of sexually transmitted infections in the UK: impact of behavior, services and interventions. *Future microbiology*. 2015;10(1):35-51.
22. Sheth P, B T. Fact sheet: sexually transmitted infections and HIV transmission. Toronto: Canadian Aids Treatment Information Exchange; 2015 [cited 2015 May 04 ]. Available from: <http://www.catie.ca/en/fact-sheets/epidemiology/sexually-transmitted-infections-and-hiv-transmission>
23. Des Jarlais DC, Arasteh K, McKnight C, Hagan H, Perlman DC, Semaan S. Associations Between Herpes Simplex Virus Type 2 and HCV With HIV Among Injecting Drug Users in New York City: The Current Importance of Sexual Transmission of HIV. *American Journal of Public Health*. 2011 01/17/accepted;101(7):1277-83. PubMed PMID: PMC3110210.
24. Des Jarlais DC, Hagan H, Arasteh K, McKnight C, Perlman D, Friedman SR. Herpes simplex virus-2 and HIV among noninjecting drug users in New York City. *Sexually transmitted diseases*. 2007;34(11):923-7.
25. Des Jarlais DC, Arasteh K, McKnight C, Perlman D, Hagan H, Semaan S, et al. Gender and age patterns in HSV-2 and HIV infection among non-injecting drug users in New York City. *Sexually transmitted diseases*. 2010;37(10):637.
26. Maxwell AE, Bastani R, Yan KX. AIDS risk behaviours and correlates in teenagers attending sexually transmitted diseases clinics in Los Angeles. *Genitourinary medicine*. 1995;71(2):82-7.
27. Muñoz-Pérez M, Rodríguez-Pichardo A, Martínez FC. Sexually transmitted diseases in 1161 HIV-positive patients: a 38-month prospective study in southern Spain. *Journal of the European Academy of Dermatology and Venereology*. 1998;11(3):221-6.
28. Allen S, Meinzen-Derr J, Kautzman M, Zulu I, Trask S, Fideli U, et al. Sexual behavior of HIV discordant couples after HIV counseling and testing. *Aids*. 2003;17(5):733-40.

29. Bolu OO, Lindsey C, Kamb ML, Kent C, Zenilman J, Douglas Jr JM, et al. Is HIV/sexually transmitted disease prevention counseling effective among vulnerable populations?: a subset analysis of data collected for a randomized, controlled trial evaluating counseling efficacy (Project RESPECT). *Sexually transmitted diseases*. 2004;31(8):469-74.
30. DiFranceisco W, Pinkerton SD, Dyatlov RV, Swain GR. Evidence of a brief surge in safer sex practices after HIV testing among a sample of high-risk men and women. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2005;39(5):606-12.
31. Kamb ML, Fishbein M, Douglas Jr JM, Rhodes F, Rogers J, Bolan G, et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. *Jama*. 1998;280(13):1161-7.
32. Weinhardt LS, Carey MP, Johnson BT, Bickham NL. Effects of HIV counseling and testing on sexual risk behavior: a meta-analytic review of published research, 1985-1997. *American journal of public health*. 1999;89(9):1397-405.
33. Des Jarlais DC, Feelemyer JP, Modi SN, Arasteh K, Hagan H. Are females who inject drugs at higher risk for HIV infection than males who inject drugs: an international systematic review of high seroprevalence areas. *Drug and alcohol dependence*. 2012;124(1):95-107.
34. Clarke S, Keenan E, Bergin C, Lyons F, Hopkins S, Mulcahy F. The changing epidemiology of HIV infection in injecting drug users in Dublin, Ireland. *HIV Medicine* 2001; 2:236 – 240.
35. Jozaghi E. Science versus politics: the need for supervised injection facilities in Montreal, Canada. *Int J Drug Policy* 2012 Sep; 23 (5): 420-1.
36. Wood E, Tyndall MW, Zhang R, Stoltz JA, Lai C, Montaner JS. Attendance at supervised injecting facilities and use of detoxification services. *N Engl J Med*. 2006 Jun 8; 354 (23):2512-4.
37. Tyndall MW, Kerr T, Zhang R, King E, Montaner JG, Wood E. Attendance, drug use patterns, and referrals made from North America's first supervised injection facility. *Drug Alcohol Depend*. 2006 Jul 27; 83(3):193-8.

## Appendices

### Appendix A: HIV case reporting form

Saskatchewan Ministry of Health		<b>HIV CASE REPORTING FORM</b>	
Complete and forward a copy in the envelope provided to the office of your regional Medical Health Officer. Use national reporting form for AIDS cases.			
This report is authorized by law. Under <i>The Public Health Act</i> it is mandatory to report all cases of HIV and AIDS to the Medical Health Officer of the regional health authority, following which mandatory information on confirmed cases will be forwarded to the Chief Medical Health Officer.			
<b>PART 1 – PATIENT INFORMATION</b>			
RHA Reporting:	<b>Check (✓) applicable</b> <input type="checkbox"/> New case report <input type="checkbox"/> Updated report	Date of Last Contact with Patient (YYYY/MM/DD):	<input type="checkbox"/> Unable to contact <input type="checkbox"/> Lost to follow-up <input type="checkbox"/> Deceased Date: _____
PHN:	Birth Date (YYYY/MM/DD):	Sex	<input type="checkbox"/> Male <input type="checkbox"/> Female <input type="checkbox"/> Other
Patient Name	Last	First	Middle
Current Street Address:	Current City/Town/First Nations Community:	Current Province:	Current Postal Code:
Street Address at time of diagnosis:	City/Town/First Nations Community at diagnosis:	Province at diagnosis:	Postal Code at diagnosis:
Country of Birth:	Arrival Year in Canada:	Ethnicity (see over for descriptions) <input type="checkbox"/> White <input type="checkbox"/> Black (N. American) <input type="checkbox"/> Arab/West Asian <input type="checkbox"/> Other, please specify: _____ <input type="checkbox"/> First Nations <input type="checkbox"/> Black (African) <input type="checkbox"/> Latin American <input type="checkbox"/> Métis <input type="checkbox"/> East Asian <input type="checkbox"/> Multiple ethnicity <input type="checkbox"/> Inuit <input type="checkbox"/> South Asian <input type="checkbox"/> Unknown	
<b>PART 2 – RISK FACTORS</b>			
<b>Sexual Risk Factors (Respond to each item)</b> <b>Y N Unknown</b> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Sex with a male <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Sex with a female  Heterosexual sex with an individual from any of the following categories: <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Person who uses injection drugs <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Bisexual male <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Transfusion recipient with documented HIV infection <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Person with a hemophilia/coagulation disorder <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Person born in a country where heterosexual transmission predominates (see over). If yes, please specify: _____  <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Person with a confirmed or suspected HIV infection or AIDS		<b>Other Risk Factors (Respond to each item)</b> <b>Y N Unknown</b> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Injected non-prescription drugs (including steroids) <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Received blood or blood components after 1985. If yes, please specify: _____ <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Occupationally exposed to HIV contaminated blood or body fluids <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Medical exposure (e.g., organ or tissue transplant, surgery, dental, oscopy). If yes, please specify: _____ <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Non medical, non-occupational exposure which could have been the source of the infection (e.g., acupuncture, tattoo, body piercing, breast milk, needle stick). If yes, please specify: _____ <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> From endemic country (see over). If yes, please specify: _____ <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Perinatal transmission <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Involved in sex trade	
Has this patient donated blood, plasma, platelets, organs, tissues, semen or breast milk? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown			
<b>PART 3 – LABORATORY/CLINICAL DATA</b>			
Lab Report Accession Number:		Specimen Collection Date (YYYY/MM/DD):	
Is this the first positive HIV test for this person? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		City, province, country of first positive HIV test, if outside of Saskatchewan:	
If no, Date of first positive (YYYY/MM/DD): _____			
Date of last negative HIV test (including last non-reactive HIV POC Test) if known? (YYYY/MM/DD):			
Is there a history of seroconversion illness? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		If yes, Date (if known)? (YYYY/MM/DD):	
Does this person have AIDS? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		Is this person pregnant? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown If yes approx # of weeks: _____	
Reason for current HIV test (Check (✓) all that apply)			
<input type="checkbox"/> Immigration/visa requirement <input type="checkbox"/> Needle stick injury, blood/body fluid exposure <input type="checkbox"/> History of a known risk factor, specify: _____		<input type="checkbox"/> Prenatal screening <input type="checkbox"/> Symptomatic for disease <input type="checkbox"/> STI screening <input type="checkbox"/> Insurance requirement <input type="checkbox"/> Other, specify: _____	
Initial CD4 count: _____ Date (YYYY/MM/DD):		Initial viral load: _____ Date (YYYY/MM/DD):	
Has this person ever had a tuberculin (PPD) skin test? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		If yes Date (YYYY/MM/DD): _____ Size in mm? _____	
If no, was anergy tested? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown			
Positive Hep B Antigen? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown If yes, Year? _____		Positive Hep C Antigen? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown If yes, Year? _____	
<b>PART 4 – ADDITIONAL INFORMATION OR COMMENTS</b>			
Reporting physician's name (please PRINT):		City/town:	Phone number:
Name of person completing this form (please PRINT):		Date report completed (YYYY/MM/DD):	Phone number:

Revised November, 2012

## Appendix B: Ethnicity description

### Ethnicity Descriptions:

**White:** People of Caucasian ethnic origins (e.g., British Isles, European, white African origins, etc.)

**First Nations:** North American Indian regardless of treaty status, living on and/or off reserve

**Métis:** A person who self-identifies as Métis

**Black North American:** North American or Caribbean black origins

**Black African:** African-born black origins

**East Asian:** e.g., Chinese, Japanese, Vietnamese, Cambodian, Indonesian, Laotian, Korean, Filipino, etc.

**South Asian:** e.g., East Indian, Pakistani, Punjabi, Bangladeshi, etc.

**Arab/West Asian:** e.g., Armenian, Egyptian, Iranian, Lebanese, Moroccan, etc.

**Latin American:** e.g., Mexican, Central/South American, etc.

**Multiple Ethnicity:** Prodigy of dual origin parentage (not Métis)

**Endemic Country Definition:** An endemic country is defined as a country where the predominant near transmission is heterosexual contact.

### **List of Endemic Countries:**

#### **Caribbean and Central/South America:**

Anguilla	French Guiana	Netherland Antilles
Antigua and Barbuda	Grenada	Saint Lucia
Bahamas	Guadeloupe	St. Kitts and Nevis
Barbados	Guyana	St. Vincent and the Grenadines
Bermuda	Haiti	Suriname
British Virgin Islands	Honduras	Trinidad and Tobago
Cayman Islands	Jamaica	Turks and Caicos Islands
Dominica	Martinique	U.S. Virgin Islands
Dominican Republic	Montserrat	

#### **Africa:**

Angola	Gambia	Rwanda
Benin	Ghana	Senegal
Botswana	Guinea	Sierra Leone
Burkina Faso	Guinea-Bissau	Somalia
Burundi	Ivory Coast	South Africa
Cameroon	Kenya	Sudan
Cape Verde	Lesotho	Swaziland
Central African Republic	Liberia	Tanzania
Chad	Malawi	Togo
Democratic Republic of the Congo	Mali	Uganda
Djibouti	Mozambique	Zambia
Equatorial Guinea	Namibia	Zimbabwe
Eritrea	Niger	
Ethiopia	Nigeria	
Gabon	Republic of Congo	

#### **Asia:**

Cambodia  
Myanmar/Burma  
Thailand

## Appendix C. Exposure category (Risk actor) hierarchy

HIV Case Report Form – Interpretation of Risks and How to Document Risks in iPHIS  
November 2012

Risk on Case Report Form (CRF)	Interpretation – Risks Associated with Transmission of HIV in this Client	Which Risk to Document in iPHIS
Sex with a male	The case has sex with a male (can be homosexual or heterosexual sex).	Use in conjunction with demographic info of the case and enter as: <ul style="list-style-type: none"> <li>HIV – Sex with a partner of the same sex or</li> <li>HIV – Heterosexual contact (no other risk) if there are not other risks identified for the case on the CRF</li> </ul>
Sex with a female	The case has sex with a female (can be homosexual or heterosexual sex).	As Above
Heterosexual sex with an individual from any of the following categories:	The case's risk for the following bullets is "Heterosexual Sex". The intent is to determine the risks of their heterosexual contacts as noted below:	All of the following are documented regarding the risk of the heterosexual contact of the case on the CRF. iPHIS does not always differentiate between heterosexual contact or sexual contact with the same sex
<ul style="list-style-type: none"> <li>Person who uses injection drugs</li> </ul>	The case's heterosexual contact(s) is a person who injects drugs	HIV – Heterosexual contact with an IDU
<ul style="list-style-type: none"> <li>Bisexual male</li> </ul>	The case's heterosexual contact(s) is a bisexual male. This should risk should only be indicated for female cases.	HIV – Heterosexual contact of a bisexual male
<ul style="list-style-type: none"> <li>Transfusion recipient with documented HIV infection</li> </ul>	The case's heterosexual contact(s) is a person who has received a transfusion and who has documented HIV infection	HIV – Sexual contact with a confirmed/suspected HIV/AIDS (MSM or heterosexual)
<ul style="list-style-type: none"> <li>Person with a hemophilia/coagulation disorder</li> </ul>	The case's heterosexual contact(s) is a person with a bleeding disorder	
<ul style="list-style-type: none"> <li>Person born in a country where heterosexual transmission predominates (see over). If yes, please specify:</li> </ul>	The case's heterosexual contact(s) is a person that was born in a country where heterosexual transmission predominates.	HIV – Heterosexual contact with a person from an HIV endemic country
<ul style="list-style-type: none"> <li>Person with a confirmed or suspected HIV infection or AIDS</li> </ul>	The case's heterosexual contact(s) is a person who has confirmed or suspected HIV infection or AIDS	HIV – Sexual contact with a confirmed/suspected HIV/AIDS (MSM or heterosexual)
	<b>The following risks relate to the case directly (not their partners as noted above)</b>	
Injected non-prescription drugs (including steroids)	The case has injected non-prescription drugs	HIV – Injection Drug Use (current or past history)
Received blood or blood components after	The case has received blood or blood components	HIV – Received blood or blood components after

1985. If yes, please specify:	after 1985. 1985 is when Canadian Blood Services started screening donations.	1985
Occupationally exposed to HIV contaminated blood or body fluids	Exposure to HIV contaminated blood or body fluids, or concentrated virus in an occupational setting. This is intended to be used for cases that have been exposed to a <u>confirmed HIV source</u> in their occupational setting.	HIV – Occupationally exposed to HIV contaminated blood or body fluids
Medical exposure (e.g., organ or tissue transplant, surgery, dental, oscopy). If yes, please specify:	The case has been exposed to HIV while undergoing a medical procedure. This is inclusive of exposure through contaminated instruments or exposure from a positive source.	HIV – Medical exposure (e.g. surgery, dental, oscopy). Please specify the procedure, location and date)
Non medical, non-occupational exposure which could have been the source of the infection (e.g., acupuncture, tattoo, body piercing, breast milk). If yes, please specify:	The case has had an exposure to the non-medical procedure noted in a non-sterile environment.	HIV – non-medical exposure (e.g. tattoo, aggravated contact with blood). Please specify the exposure event, location and approximate date.
From endemic country (see over). If yes, please specify:	The case is from an endemic country	HIV – from endemic country – please specify Country from
Perinatal transmission	The case is an infant who was born to an HIV positive woman. Transmission may have occurred in utero or during childbirth.	HIV – perinatal transmission
Involved in sex trade	Case either offers or receives food, money, shelter, drugs for sex	HIV – Sex Trade Worker

In Canada, primary risk is assigned to an individual with multiple risks. This shows the most likely route of transmission. Primary risk uses a hierarchy of risk to assign probable exposure category, with the aid of the following ranking (highest to lowest):

Perinatal transmission

IDU

MSM & IDU

MSM

Endemic Country

Heterosexual Sex

Please note that assigning primary transmission risk does not necessarily mean transmission occurred by that exposure category. For instance, an individual who is engaged in sex work, who also practices injection drug and heterosexual, would be assigned the primary transmission risk IDU since it is the highest in the hierarchy. Yet, it is possible that HIV transmission occurred via heterosexual sex. As a result of this, it is better to include all risk factors in predictive a modeling.



## **Appendix D: MEDLINE search strategy**

1. exp sexually transmitted diseases/
2. HIV.mp. or exp human immunodeficiency viruses/
3. (HIV infections or Human immunodeficiency viruses).sh. or human immunodeficiency syndrome.mp. or HIV-1 infections.sh. or acquired immune deficiency syndrome.sh. or Human immunodeficiency virus 1.od.
4. human immun\*.mp.
5. HIV infection.mp. or exp HIV infections/
6. (Human immunodeficiency viruses or HIV infections).sh. or HIV infect\*.mp.
7. HIV prevalence.mp. or human immunodeficiency viruses.sh. or HIV infections.sh. or seroprevalence.sh.
8. AIDS.mp. or exp acquired immune deficiency syndrome/
9. acquire immunodeficiency syndrome.mp. or human immunodeficiency viruses.sh. or acquired immune deficiency syndrome.sh. or HIV infections.sh.
10. 2or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. injecting drug abuse.mp. or exp injecting drug abuse/
12. (drug abuse or injecting drug abuse).sh. or intravenous drug abuse.mp. or injecting drug users.sh.
13. injecting drug user.mp. or exp injecting drug users/
14. injecting drug users.sh. or IDU.mp. or injecting drug abuse.sh. or needle sharing.sh.
15. injecting drug users.sh. or substance abuse injection.mp. or injecting drug abuse.sh.
16. inject\* drug abuse.mp. or injecting drug abuse.sh. or injecting drug users.sh. or drug addiction.sh. or needle exchange schemes.sh.
17. substance abuse inject\*.mp. or substance abuse.sh.
18. heroin.sh. or heroine.mp.
19. drug addiction.sh. or heroine dependence.mp. or drug abuse.sh.

20. drug addiction.mp. or exp drug addiction/
21. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. exp females/ or female.mp.
23. male.mp. or exp males/
24. developed country.mp. or exp Developed Countries/
25. developed nation.mp.
26. 24 or 25
27. portugal.mp. or exp Portugal/
28. spain.mp. or exp Spain/
29. united kingdom.mp. or exp UK/
30. exp South Australia/ or australia.mp. or exp Australia/ or exp Western Australia/
31. exp France/ or exp Central France/ or france.mp.
32. austria.mp. or exp Austria/
33. "Irish Republic AND/OR Northern Ireland"/
34. italy.mp. or exp Italy/
35. exp Netherlands/ or netherland.mp.
- 36 sweden.mp. or exp Sweden/
37. USA.gl. or united states.mp.
38. canada.mp. or exp Canada/
39. estonia.mp. or exp Estonia/
40. latvia.mp. or exp Latvia/
41. belgium.mp. or exp Belgium/
42. denmark.mp. or exp Denmark/
43. exp Finland/ or finland.mp.

44. germany.mp. or exp Germany/
45. greece.mp. or exp Greece/
46. luxembourg.mp. or exp Luxembourg/
47. bulgaria.mp. or exp Bulgaria/
48. croatia.mp. or exp Croatia/
49. exp Japan/ or japan.mp.
50. new zealand.mp. or exp New Zealand/
51. exp Iceland/ or iceland.mp.
52. norway.mp. or exp Norway/
53. switzerland.mp. or exp Switzerland/
54. slovenia.mp. or exp Slovenia/
55. slovakia.mp. or exp Slovakia/
56. romania.mp. or exp Romania/
57. poland.mp. or exp Poland/
58. malta.mp. or exp Malta/
59. lithuania.mp. or exp Lithuania/
60. hungary.mp. or exp Hungary/
61. czech republic.mp. or exp Czech Republic/
62. cyprus.mp. or exp Cyprus/
63. sexually transmitted diseases.mp. or exp sexually transmitted diseases/
64. Sexually Transmitted infections.mp. or exp sexually transmitted diseases/
65. STI.mp. or syphilis.sh. or Treponema pallidum.od. or Chlamydia trachomatis.od. or disease prevalence.sh. or sexually transmitted diseases.sh.
66. std.mp. or Chlamydia trachomatis.od. or sexually transmitted diseases.sh.
67. exp syphilis/ or Syphilis.mp.

68. *Treponema pallidum*.od. or bacterial diseases.sh. or syphilis.sh. or Chancre.mp. or sexually transmitted diseases.sh.
69. *Treponema pallidum*.mp. or exp *Treponema pallidum*/
70. chancroid.mp. or exp chancroid/
71. *Haemophilus ducreyi*.mp. or exp *Haemophilus ducreyi*/
72. disease prevalence.sh. or *Neisseria gonorrhoeae*.od. or Gonorrhea.mp. or syphilis.sh. or *Treponema pallidum*.od. or sexually transmitted diseases.sh. or gonorrhoea.sh. or *Chlamydia trachomatis*.od. or bacterial diseases.sh.
73. *Neisseria Gonorrhoeae*.mp. or exp *Neisseria gonorrhoeae*/
74. sexually transmitted diseases.sh. or *Chlamydia*.od. or *Chlamydia infections*.mp. or bacterial diseases.sh. or *Chlamydia trachomatis*.od. or disease prevalence.sh.
75. *Chlamydia trachomatis*.mp. or exp *Chlamydia trachomatis*/
76. (sexually transmitted diseases or herpes simplex viruses).sh. or Herpes genitalis.mp. or herpes simplex.sh. or Human herpesvirus 2.od. or herpes simplex genitalis.sh.
77. Herpes Simplex.mp. or exp herpes simplex/
78. Herpesvirus 2.mp.
79. Lymphogranuloma venereum.mp. or sexually transmitted diseases.sh. or bacterial diseases.sh. or disease prevalence.sh. or *Chlamydia trachomatis*.od.
80. *Trichomonas vaginitis*.mp. or trichomoniasis.sh. or bacterial diseases.sh. or sexually transmitted diseases.sh. or *Trichomonas vaginalis*.od.
81. 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80
82. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62
83. 26 or 82
84. 1 or 81

85. 22 and 23

86. 10 and 83 and 84 and 85

87. 10 and 21 and 83 and 84

88. limit 87 to (humans and yr="1985 - 2016")

89. limit 88 to english language

90. limit 86 to humans

91. limit 90 to yr="1985 -Current"

92. limit 91 to english language

## Appendix E : Quality assesement tool for quantitative studies

### QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES



#### COMPONENT RATINGS

##### A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

- 1 Very likely
- 2 Somewhat likely
- 3 Not likely
- 4 Can't tell

(Q2) What percentage of selected individuals agreed to participate?

- 1 80 - 100% agreement
- 2 60 – 79% agreement
- 3 less than 60% agreement
- 4 Not applicable
- 5 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

##### B) STUDY DESIGN

Indicate the study design

- 1 Randomized controlled trial
- 2 Controlled clinical trial
- 3 Cohort analytic (two group pre + post)
- 4 Case-control
- 5 Cohort (one group pre + post (before and after))
- 6 Interrupted time series
- 7 Other specify \_\_\_\_\_
- 8 Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)

No Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

**C) CONFOUNDERS**

**(Q1) Were there important differences between groups prior to the intervention?**

- 1 Yes
- 2 No
- 3 Can't tell

**The following are examples of confounders:**

- 1 Race
- 2 Sex
- 3 Marital status/family
- 4 Age
- 5 SES (income or class)
- 6 Education
- 7 Health status
- 8 Pre-intervention score on outcome measure

**(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?**

- 1 80 – 100% (most)
- 2 60 – 79% (some)
- 3 Less than 60% (few or none)
- 4 Can't Tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

**D) BLINDING**

**(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?**

- 1 Yes
- 2 No
- 3 Can't tell

**(Q2) Were the study participants aware of the research question?**

- 1 Yes
- 2 No
- 3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

**E) DATA COLLECTION METHODS**

**(Q1) Were data collection tools shown to be valid?**

- 1 Yes
- 2 No
- 3 Can't tell

**(Q2) Were data collection tools shown to be reliable?**

- 1 Yes
- 2 No
- 3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

**F) WITHDRAWALS AND DROP-OUTS**

**(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?**

- 1 Yes
- 2 No
- 3 Can't tell
- 4 Not Applicable (i.e. one time surveys or interviews)

**(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).**

- 1 80 -100%
- 2 60 - 79%
- 3 less than 60%
- 4 Can't tell
- 5 Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK	
See dictionary	1	2	3	Not Applicable

**G) INTERVENTION INTEGRITY**

**(Q1) What percentage of participants received the allocated intervention or exposure of interest?**

- 1 80 -100%
- 2 60 - 79%
- 3 less than 60%
- 4 Can't tell

**(Q2) Was the consistency of the intervention measured?**

- 1 Yes
- 2 No
- 3 Can't tell

**(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?**

- 4 Yes
- 5 No
- 6 Can't tell

**H) ANALYSES**

**(Q1) Indicate the unit of allocation (circle one)**

community   organization/institution   practice/office   individual

**(Q2) Indicate the unit of analysis (circle one)**

community   organization/institution   practice/office   individual

**(Q3) Are the statistical methods appropriate for the study design?**

- 1 Yes
- 2 No
- 3 Can't tell

**(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?**

- 1 Yes
- 2 No
- 3 Can't tell



**GLOBAL RATING****COMPONENT RATINGS**

Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

<b>A</b>	<b>SELECTION BIAS</b>	<b>STRONG</b>	<b>MODERATE</b>	<b>WEAK</b>
		1	2	3
<b>B</b>	<b>STUDY DESIGN</b>	<b>STRONG</b>	<b>MODERATE</b>	<b>WEAK</b>
		1	2	3
<b>C</b>	<b>CONFOUNDERS</b>	<b>STRONG</b>	<b>MODERATE</b>	<b>WEAK</b>
		1	2	3
<b>D</b>	<b>BLINDING</b>	<b>STRONG</b>	<b>MODERATE</b>	<b>WEAK</b>
		1	2	3
<b>E</b>	<b>DATA COLLECTION METHOD</b>	<b>STRONG</b>	<b>MODERATE</b>	<b>WEAK</b>
		1	2	3
<b>F</b>	<b>WITHDRAWALS AND DROPOUTS</b>	<b>STRONG</b>	<b>MODERATE</b>	<b>WEAK</b>
		1	2	3
				Not Applicable

**GLOBAL RATING FOR THIS PAPER (circle one):**

1      STRONG      (no WEAK ratings)  
2      MODERATE      (one WEAK rating)  
3      WEAK      (two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?

No      Yes

If yes, indicate the reason for the discrepancy

1      Oversight  
2      Differences in interpretation of criteria  
3      Differences in interpretation of study

**Final decision of both reviewers (circle one):**

**1      STRONG**  
**2      MODERATE**  
**3      WEAK**

## Appendix F: Quality assessment tool for qualitative studies dictionary

### Quality Assessment Tool for Quantitative Studies Dictionary



The purpose of this dictionary is to describe items in the tool thereby assisting raters to score study quality. Due to under-reporting or lack of clarity in the primary study, raters will need to make judgements about the extent that bias may be present. When making judgements about each component, raters should form their opinion based upon information contained in the study rather than making inferences about what the authors intended.

#### A) SELECTION BIAS

**(Q1)** Participants are more likely to be representative of the target population if they are randomly selected from a comprehensive list of individuals in the target population (score very likely). They may not be representative if they are referred from a source (e.g. clinic) in a systematic manner (score somewhat likely) or self-referred (score not likely).

**(Q2)** Refers to the % of subjects in the control and intervention groups that agreed to participate in the study before they were assigned to intervention or control groups.

#### B) STUDY DESIGN

In this section, raters assess the likelihood of bias due to the allocation process in an experimental study. For observational studies, raters assess the extent that assessments of exposure and outcome are likely to be independent. Generally, the type of design is a good indicator of the extent of bias. In stronger designs, an equivalent control group is present and the allocation process is such that the investigators are unable to predict the sequence.

##### **Randomized Controlled Trial (RCT)**

An experimental design where investigators randomly allocate eligible people to an intervention or control group. A rater should describe a study as an RCT if the randomization sequence allows each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. If the investigators do not describe the allocation process and only use the words 'random' or 'randomly', the study is described as a controlled clinical trial.

See below for more details.

*Was the study described as randomized?*

Score YES, if the authors used words such as random allocation, randomly assigned, and random assignment.

Score NO, if no mention of randomization is made.

*Was the method of randomization described?*

Score YES, if the authors describe any method used to generate a random allocation sequence.

Score NO, if the authors do not describe the allocation method or describe methods of allocation such as alternation, case record numbers, dates of birth, day of the week, and any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers of assignments.

If NO is scored, then the study is a controlled clinical trial.

### *Was the method appropriate?*

Score YES, if the randomization sequence allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. Examples of appropriate approaches include assignment of subjects by a central office unaware of subject characteristics, or sequentially numbered, sealed, opaque envelopes.

Score NO, if the randomization sequence is open to the individuals responsible for recruiting and allocating participants or providing the intervention, since those individuals can influence the allocation process, either knowingly or unknowingly.

If NO is scored, then the study is a controlled clinical trial.

#### Controlled Clinical Trial (CCT)

An experimental study design where the method of allocating study subjects to intervention or control groups is open to individuals responsible for recruiting subjects or providing the intervention. The method of allocation is transparent before assignment, e.g. an open list of random numbers or allocation by date of birth, etc.

#### Cohort analytic (two group pre and post)

An observational study design where groups are assembled according to whether or not exposure to the intervention has occurred. Exposure to the intervention is not under the control of the investigators. Study groups might be non-equivalent or not comparable on some feature that affects outcome.

#### Case control study

A retrospective study design where the investigators gather 'cases' of people who already have the outcome of interest and 'controls' who do not. Both groups are then questioned or their records examined about whether they received the intervention exposure of interest.

#### Cohort (one group pre + post (before and after))

The same group is pretested, given an intervention, and tested immediately after the intervention. The intervention group, by means of the pretest, act as their own control group.

#### Interrupted time series

A time series consists of multiple observations over time. Observations can be on the same units (e.g. individuals over time) or on different but similar units (e.g. student achievement scores for particular grade and school). Interrupted time series analysis requires knowing the specific point in the series when an intervention occurred.

## **C) CONFOUNDERS**

By definition, a confounder is a variable that is associated with the intervention or exposure and causally related to the outcome of interest. Even in a robust study design, groups may not be balanced with respect to important variables prior to the intervention. The authors should indicate if confounders were controlled in the design (by stratification or matching) or in the analysis. If the allocation to intervention and control groups is randomized, the authors must report that the groups were balanced at baseline with respect to confounders (either in the text or a table).

## **D) BLINDING**

(Q1) Assessors should be described as blinded to which participants were in the control and intervention groups. The purpose of blinding the outcome assessors (who might also be the care providers) is to protect against detection bias.

(Q2) Study participants should not be aware of (i.e. blinded to) the research question. The purpose of blinding the participants is to protect against reporting bias.

## **E) DATA COLLECTION METHODS**

Tools for primary outcome measures must be described as reliable and valid. If 'face' validity or 'content' validity has been demonstrated, this is acceptable. Some sources from which data may be collected are described below:

Self reported data includes data that is collected from participants in the study (e.g. completing a questionnaire, survey, answering questions during an interview, etc.).

Assessment/Screening includes objective data that is retrieved by the researchers. (e.g. observations by investigators).

Medical Records/Vital Statistics refers to the types of formal records used for the extraction of the data.

**Reliability and validity can be reported in the study or in a separate study. For example, some standard assessment tools have known reliability and validity.**

## **F) WITHDRAWALS AND DROP-OUTS**

Score **YES** if the authors describe BOTH the numbers and reasons for withdrawals and drop-outs.

Score **NO** if either the numbers or reasons for withdrawals and drop-outs are not reported.

The percentage of participants completing the study refers to the % of subjects remaining in the study at the final data collection period in all groups (i.e. control and intervention groups).

## **G) INTERVENTION INTEGRITY**

The number of participants receiving the intended intervention should be noted (consider both frequency and intensity). For example, the authors may have reported that at least 80 percent of the participants received the complete intervention. The authors should describe a method of measuring if the intervention was provided to all participants the same way. As well, the authors should indicate if subjects received an unintended intervention that may have influenced the outcomes. For example, co-intervention occurs when the study group receives an additional intervention (other than that intended). In this case, it is possible that the effect of the intervention may be over-estimated. Contamination refers to situations where the control group accidentally receives the study intervention. This could result in an under-estimation of the impact of the intervention.

## **H) ANALYSIS APPROPRIATE TO QUESTION**

Was the quantitative analysis appropriate to the research question being asked?

An intention-to-treat analysis is one in which all the participants in a trial are analyzed according to the intervention to which they were allocated, whether they received it or not. Intention-to-treat analyses are favoured in assessments of effectiveness as they mirror the noncompliance and treatment changes that are likely to occur when the intervention is used in practice, and because of the risk of attrition bias when participants are excluded from the analysis.



### **Component Ratings of Study:**

For each of the six components A – F, use the following descriptions as a roadmap.

#### **A) SELECTION BIAS**

**Strong:** The selected individuals are very likely to be representative of the target population (Q1 is 1) **and** there is greater than 80% participation (Q2 is 1).

**Moderate:** The selected individuals are at least somewhat likely to be representative of the target population (Q1 is 1 or 2); **and** there is 60 - 79% participation (Q2 is 2). 'Moderate' may also be assigned if Q1 is 1 or 2 and Q2 is 5 (can't tell).

**Weak:** The selected individuals are not likely to be representative of the target population (Q1 is 3); **or** there is less than 60% participation (Q2 is 3) **or** selection is not described (Q1 is 4); and the level of participation is not described (Q2 is 5).

#### **B) DESIGN**

**Strong:** will be assigned to those articles that described RCTs and CCTs.

**Moderate:** will be assigned to those that described a cohort analytic study, a case control study, a cohort design, or an interrupted time series.

**Weak:** will be assigned to those that used any other method or did not state the method used.

#### **C) CONFOUNDERS**

**Strong:** will be assigned to those articles that controlled for at least 80% of relevant confounders (Q1 is 2); **or** (Q2 is 1).

**Moderate:** will be given to those studies that controlled for 60 – 79% of relevant confounders (Q1 is 1) **and** (Q2 is 2).

**Weak:** will be assigned when less than 60% of relevant confounders were controlled (Q1 is 1) **and** (Q2 is 3) **or** control of confounders was not described (Q1 is 3) **and** (Q2 is 4).

#### **D) BLINDING**

**Strong:** The outcome assessor is not aware of the intervention status of participants (Q1 is 2); **and** the study participants are not aware of the research question (Q2 is 2).

**Moderate:** The outcome assessor is not aware of the intervention status of participants (Q1 is 2); **or** the study participants are not aware of the research question (Q2 is 2); **or** blinding is not described (Q1 is 3 and Q2 is 3).

**Weak:** The outcome assessor is aware of the intervention status of participants (Q1 is 1); **and** the study participants are aware of the research question (Q2 is 1).

#### **E) DATA COLLECTION METHODS**

**Strong:** The data collection tools have been shown to be valid (Q1 is 1); **and** the data collection tools have been shown to be reliable (Q2 is 1).

**Moderate:** The data collection tools have been shown to be valid (Q1 is 1); **and** the data collection tools have not been shown to be reliable (Q2 is 2) **or** reliability is not described (Q2 is 3).

**Weak:** The data collection tools have not been shown to be valid (Q1 is 2) **or** both reliability and validity are not described (Q1 is 3 and Q2 is 3).

#### **F) WITHDRAWALS AND DROP-OUTS - a rating of:**

**Strong:** will be assigned when the follow-up rate is 80% or greater (Q2 is 1).

**Moderate:** will be assigned when the follow-up rate is 60 – 79% (Q2 is 2) **OR** Q2 is 5 (N/A).

**Weak:** will be assigned when a follow-up rate is less than 60% (Q2 is 3) or if the withdrawals and drop-outs were not described (Q2 is 4).